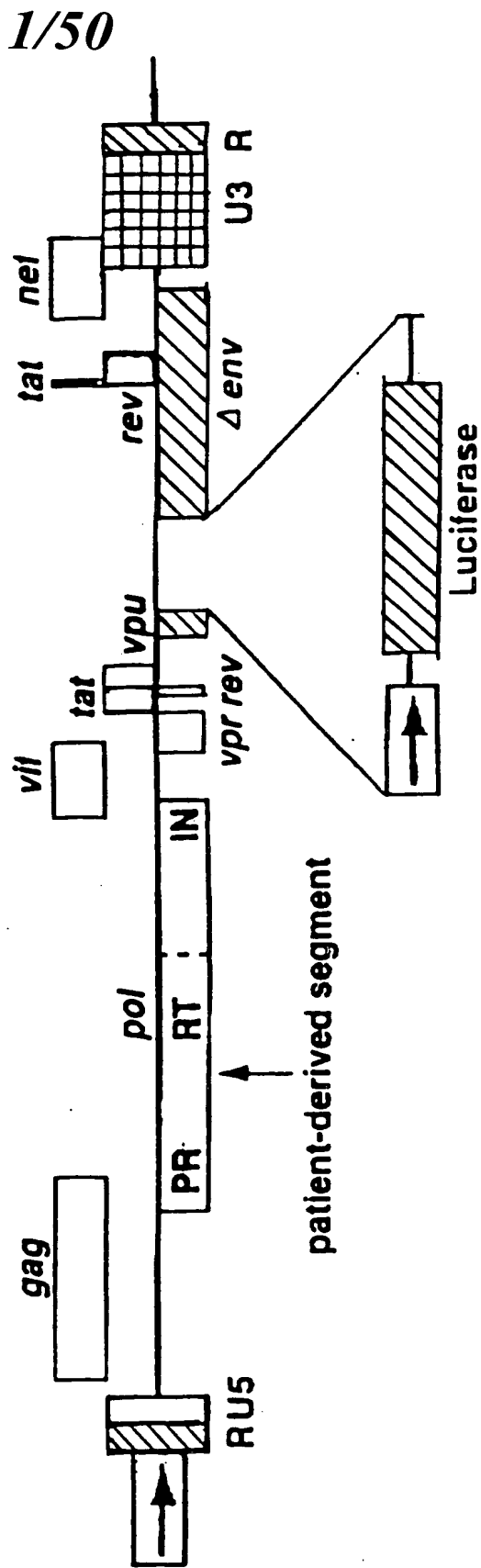




FIGURE 1

PhenoSense™ HIV Resistance Test Vector.

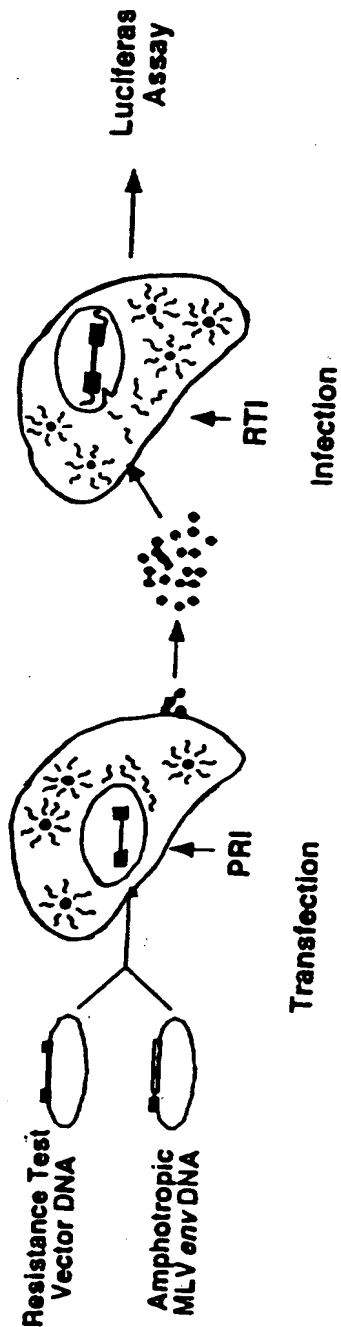




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FIGURE 2

*PhenoSense™ HIV Schematic Diagram.*





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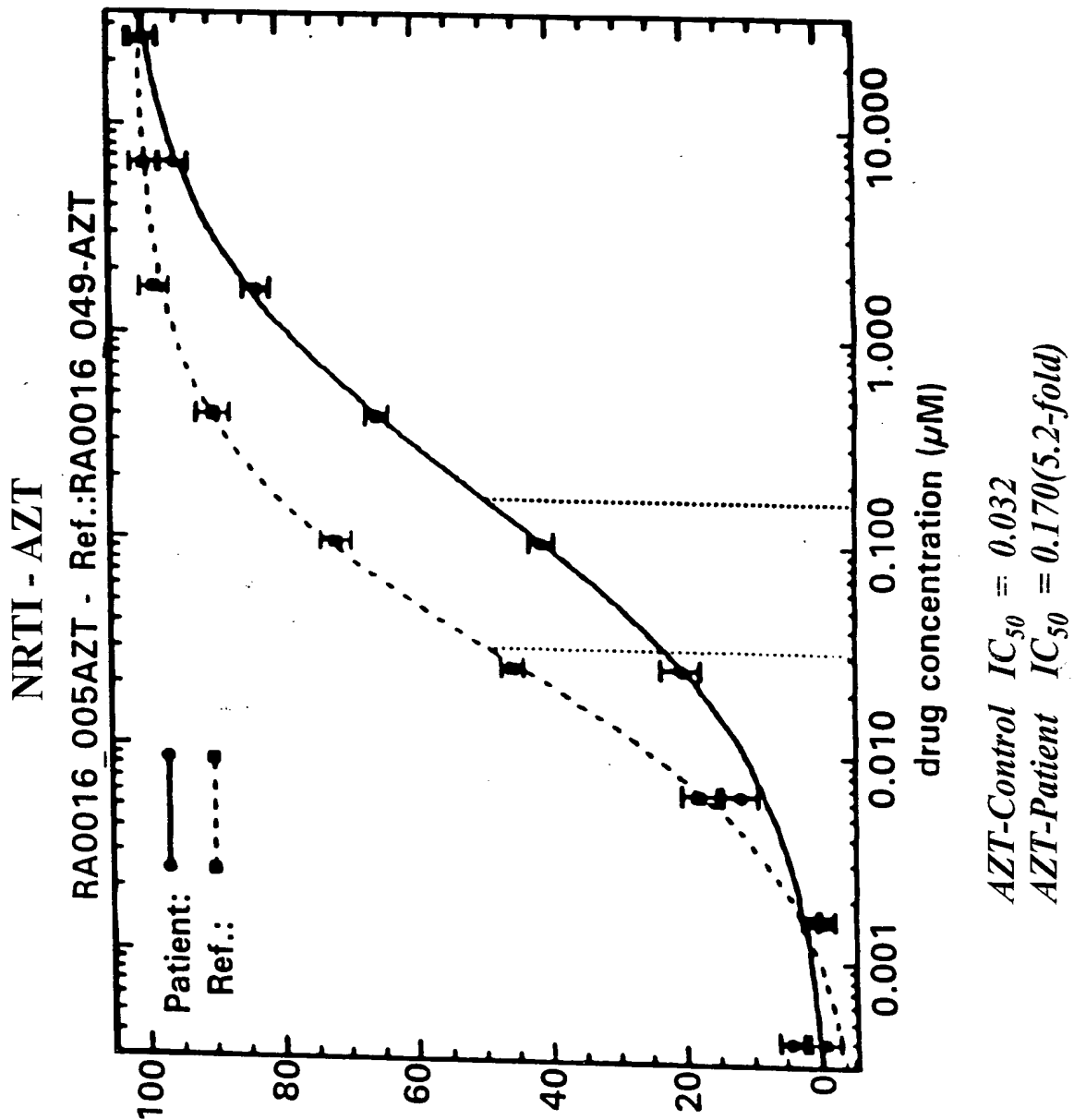
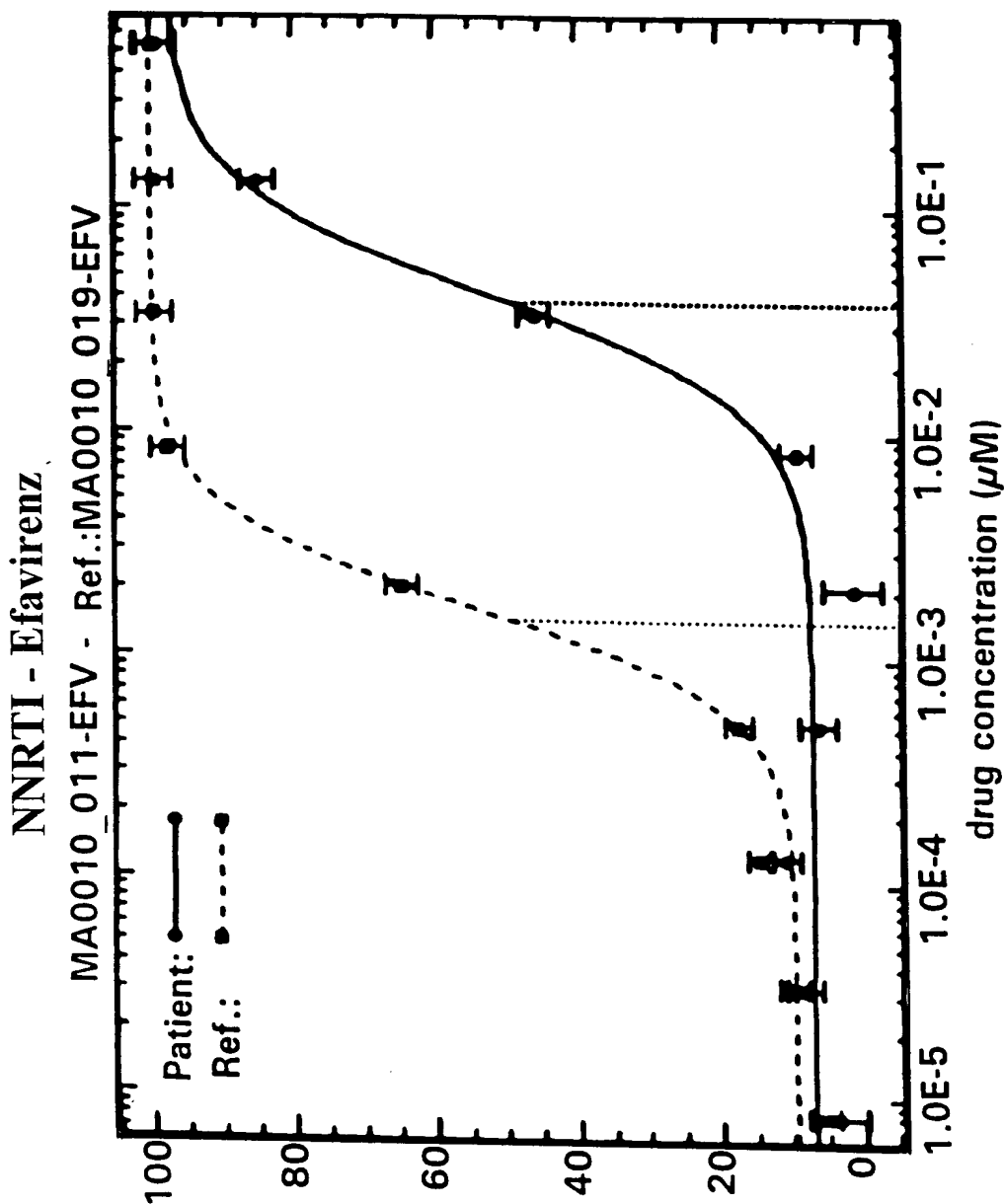


FIGURE 3A



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EFV-Control  $IC_{50} = 0.0015$   
EFV-Patient  $IC_{50} = 0.0380(25.6\text{-fold})$



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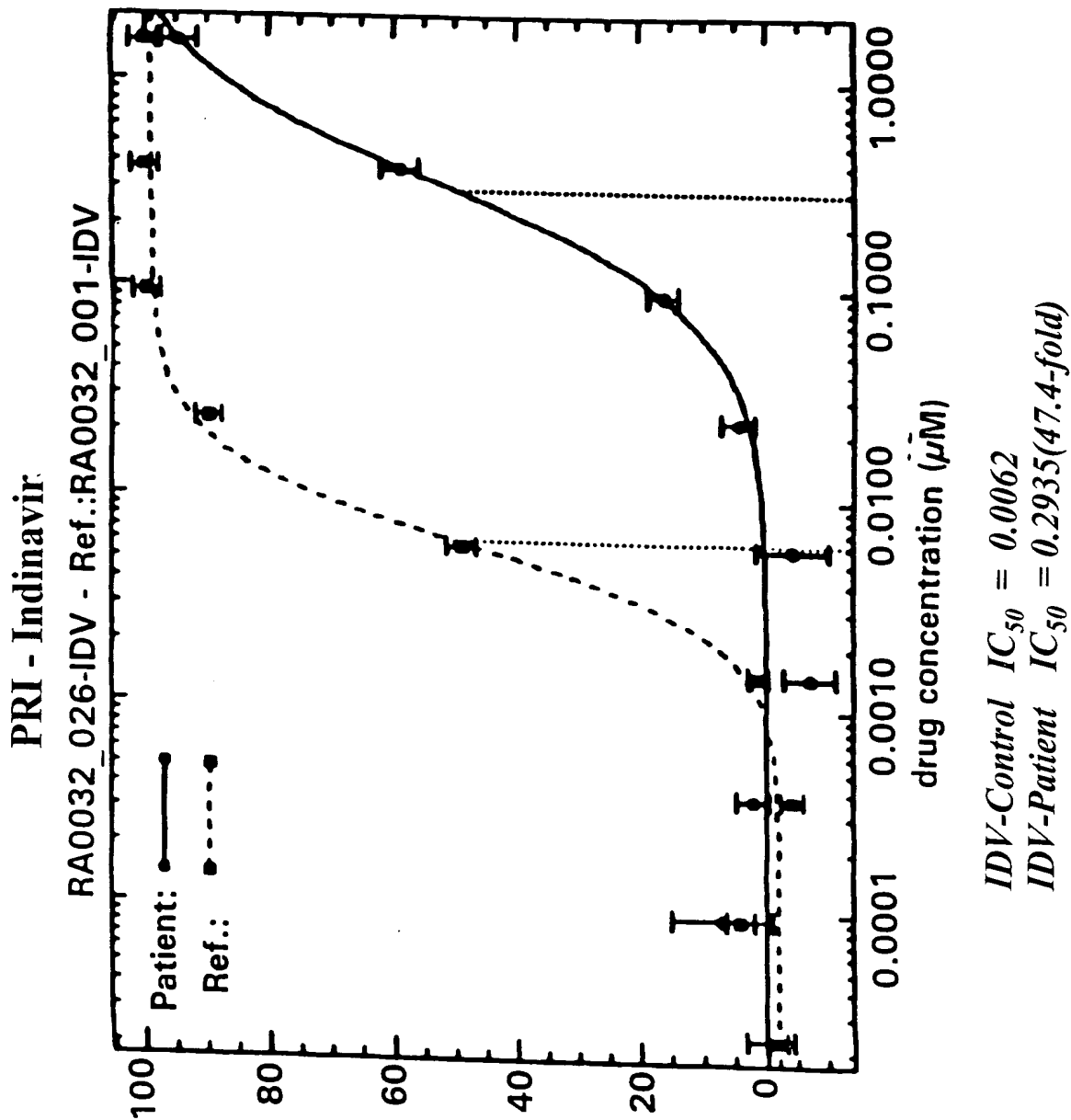


FIGURE 3C



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FIGURE 4A

SQV

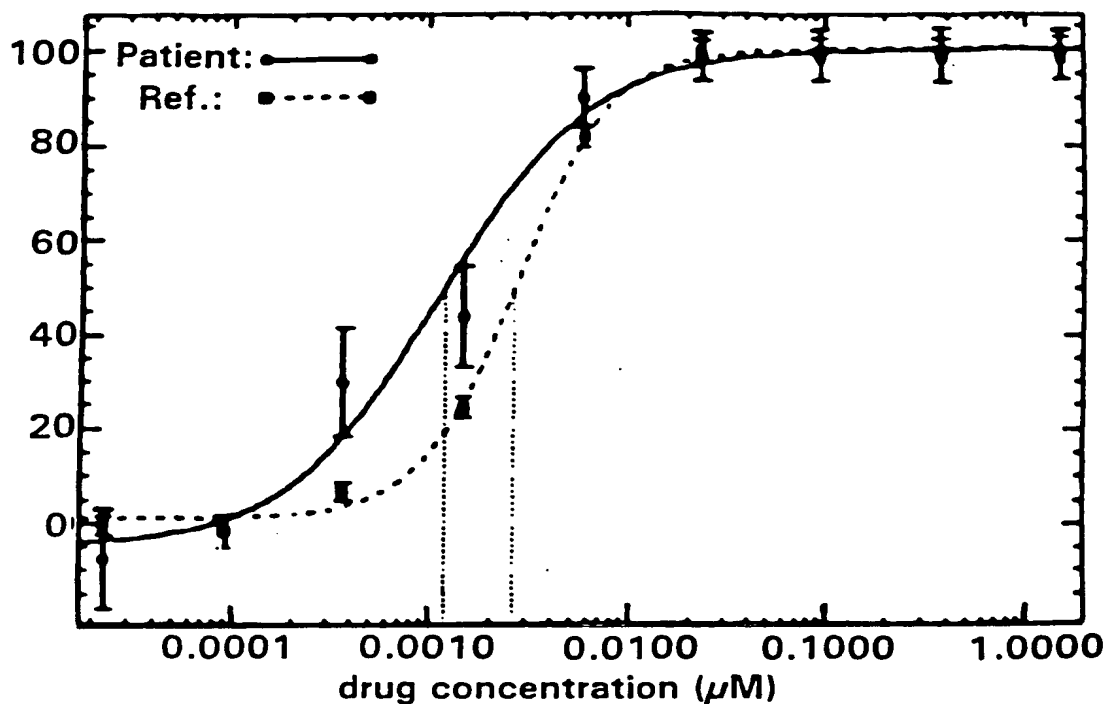
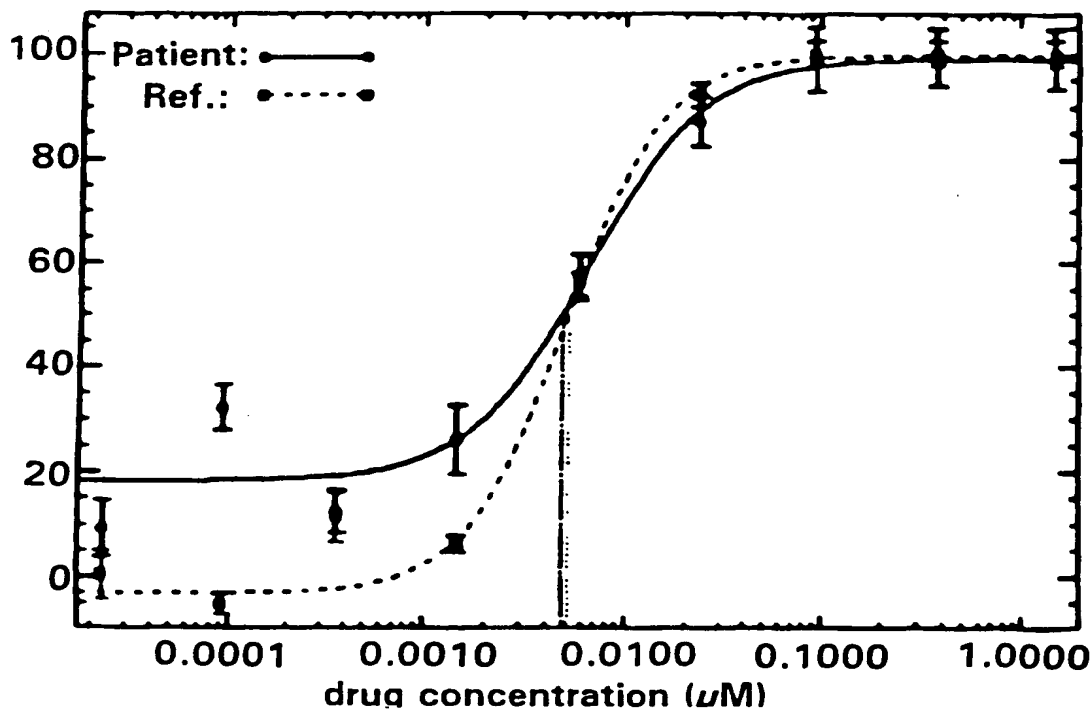


FIGURE 4B

IDV





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FIGURE 4C

RTV

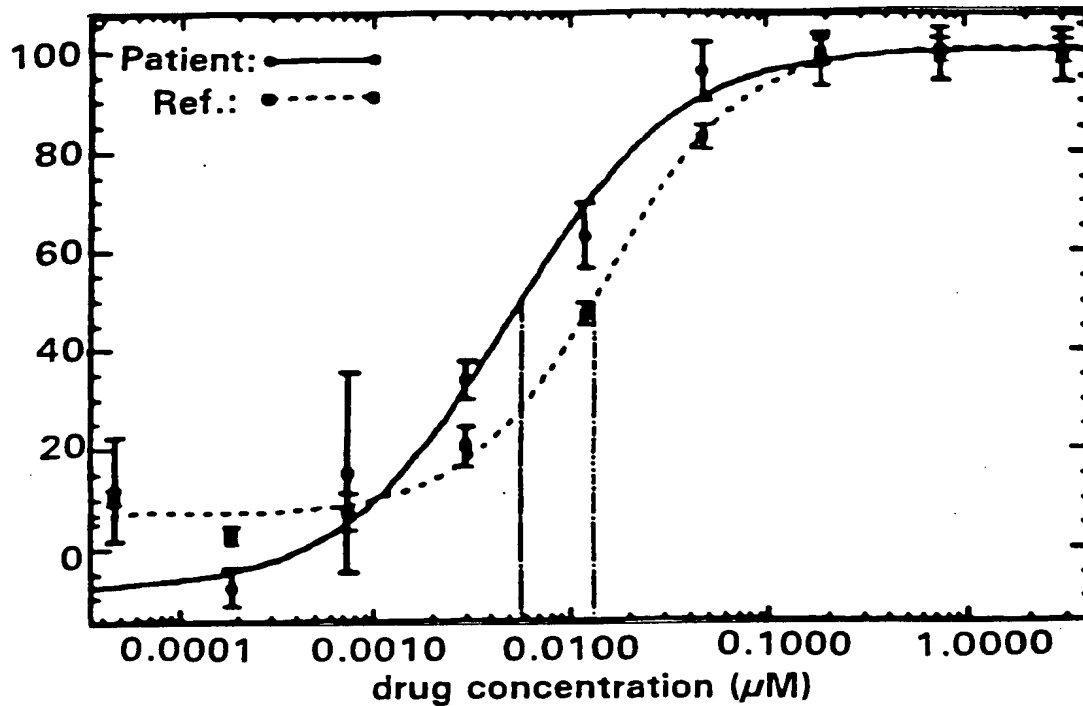
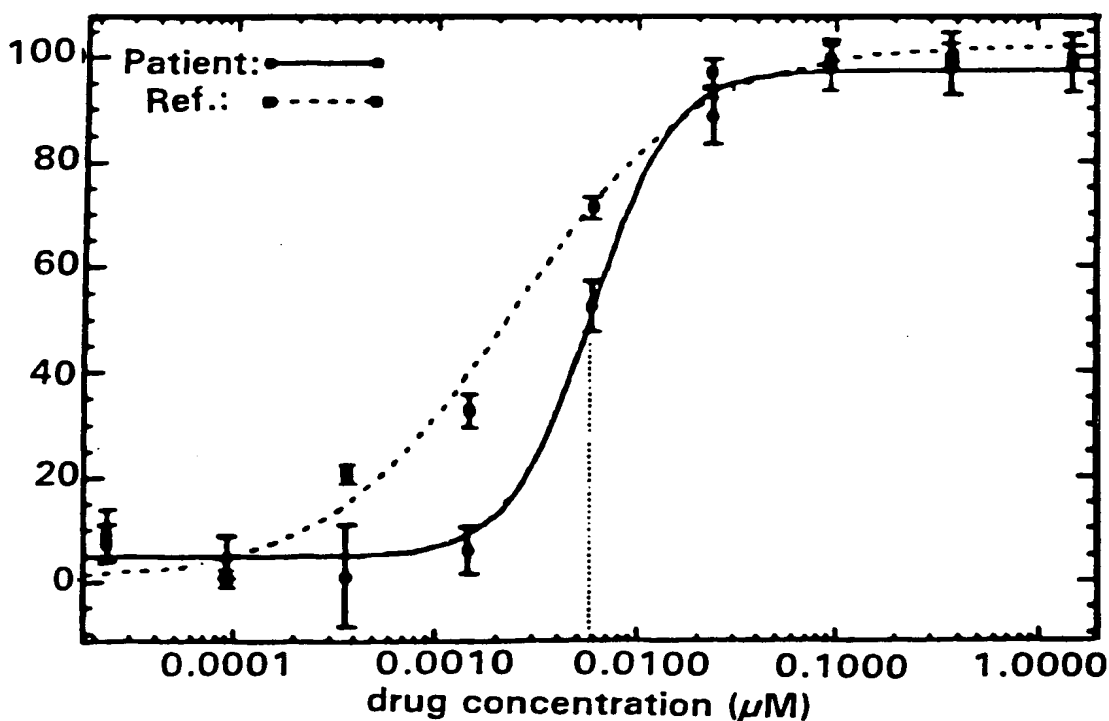


FIGURE 4D

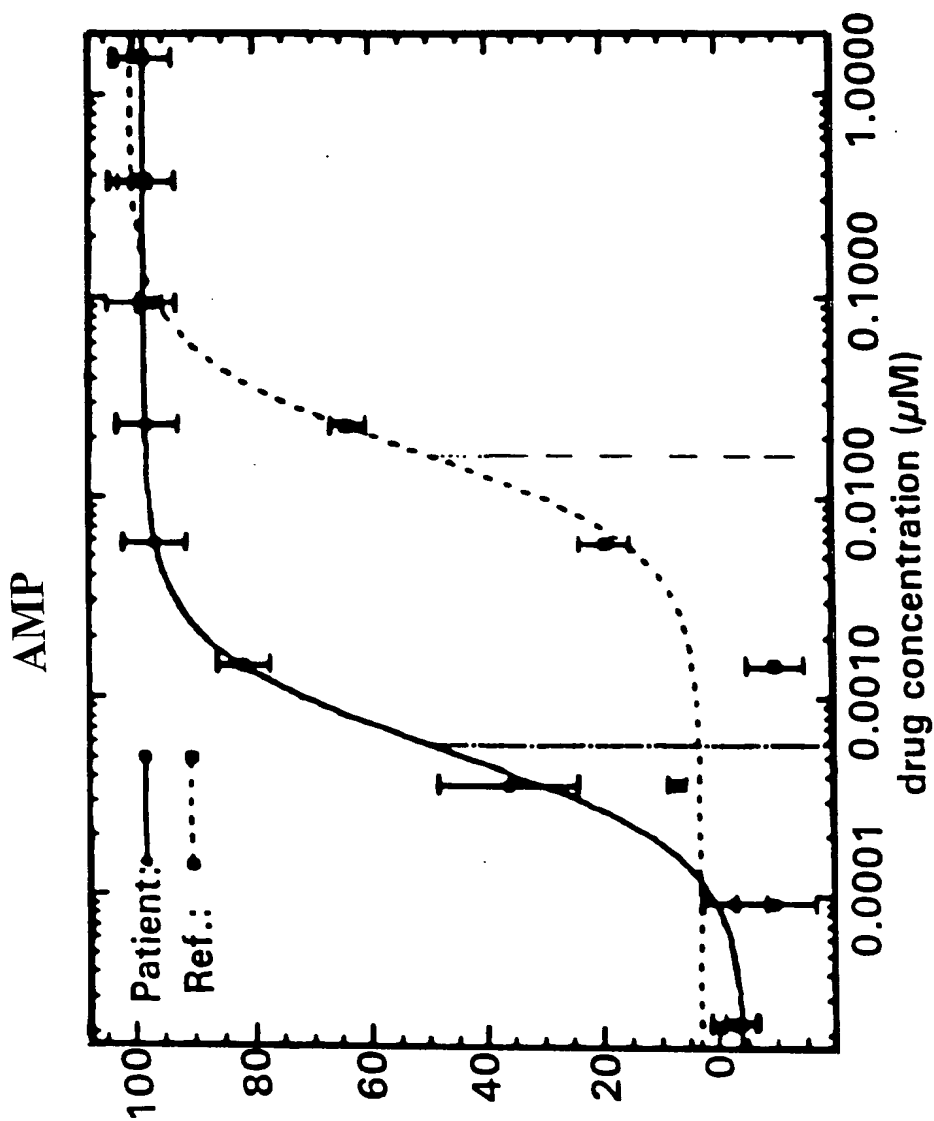
NFV





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FIGURE 4E







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FIGURE 5A

SQV

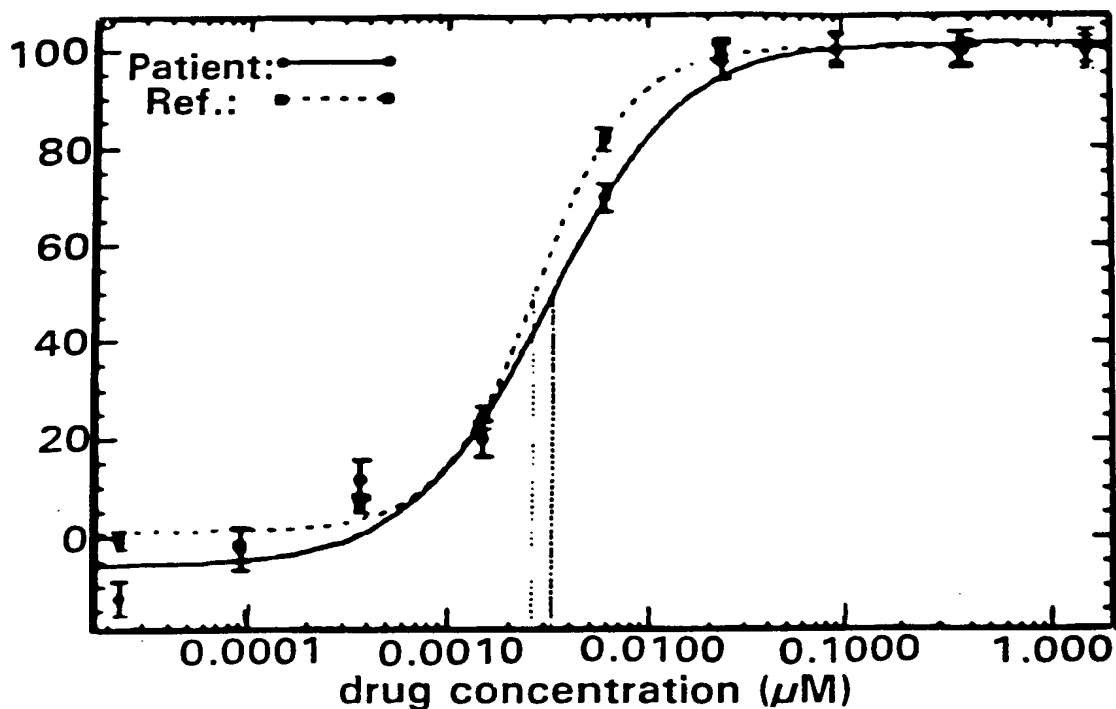
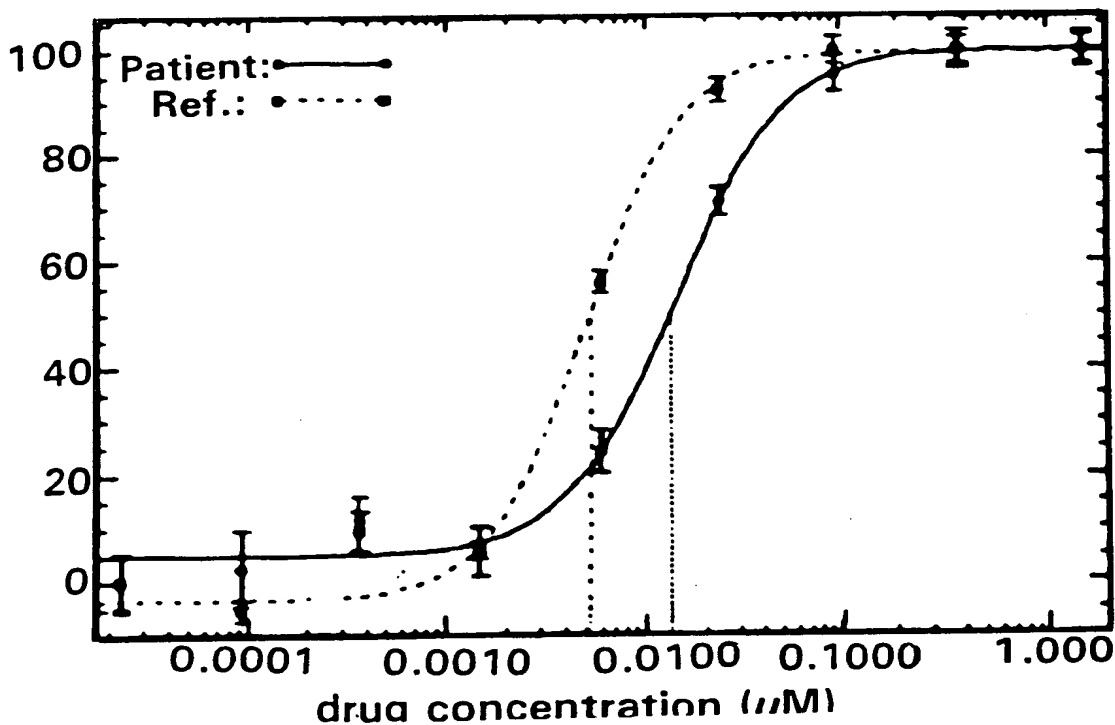


FIGURE 5B

IDV





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FIGURE 5C

RTV

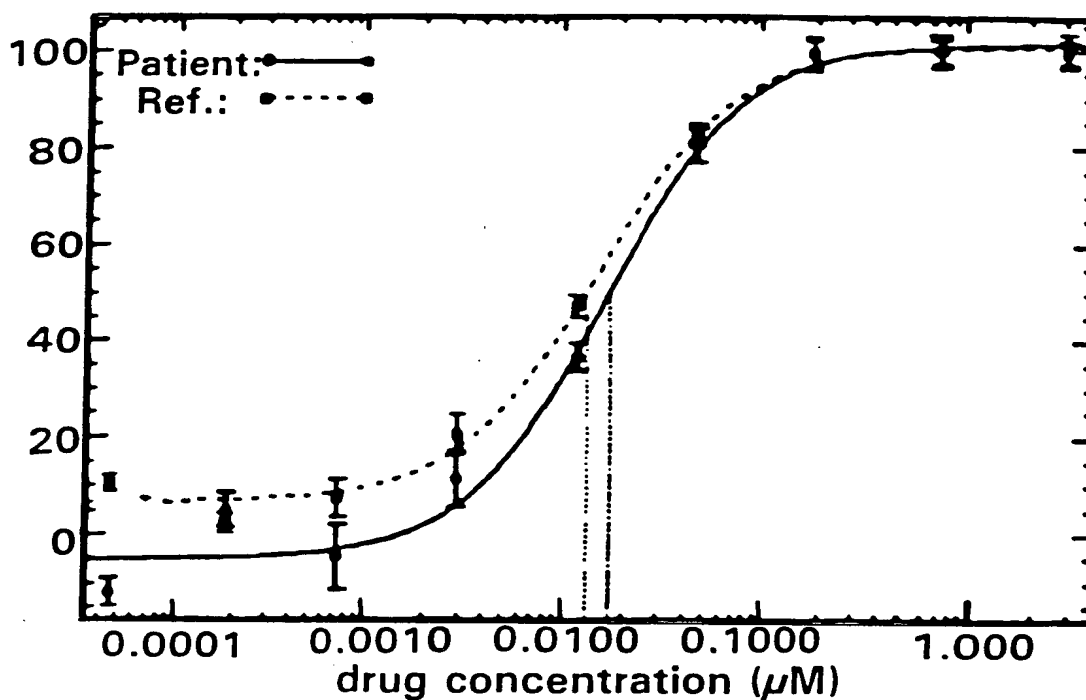
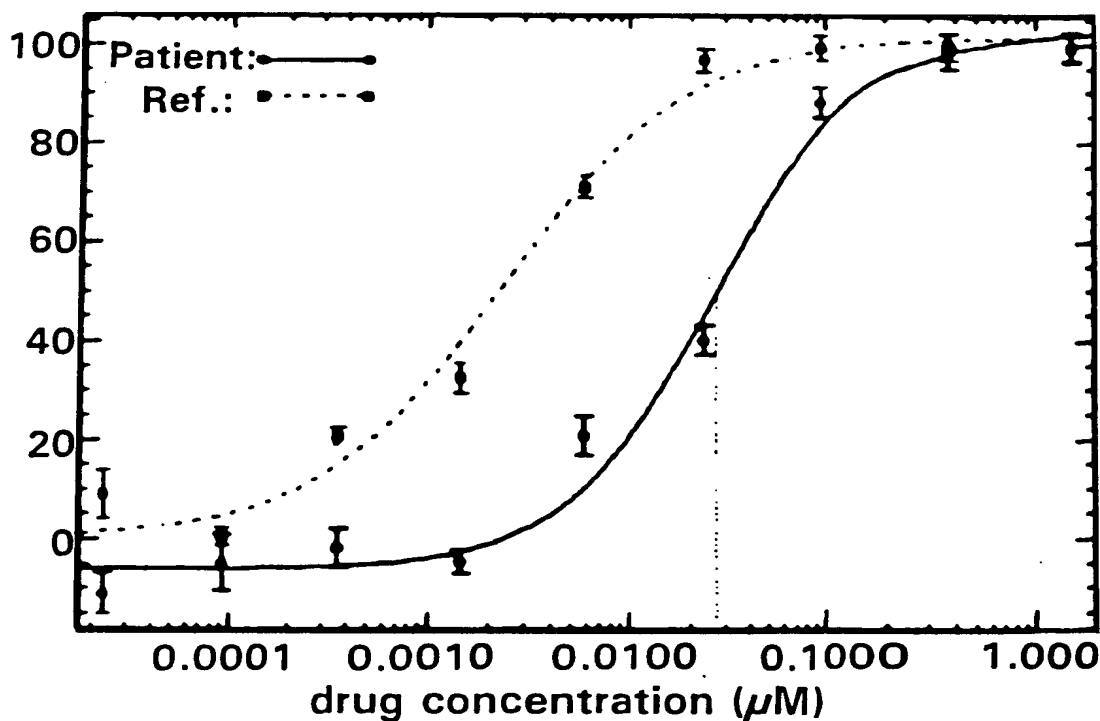


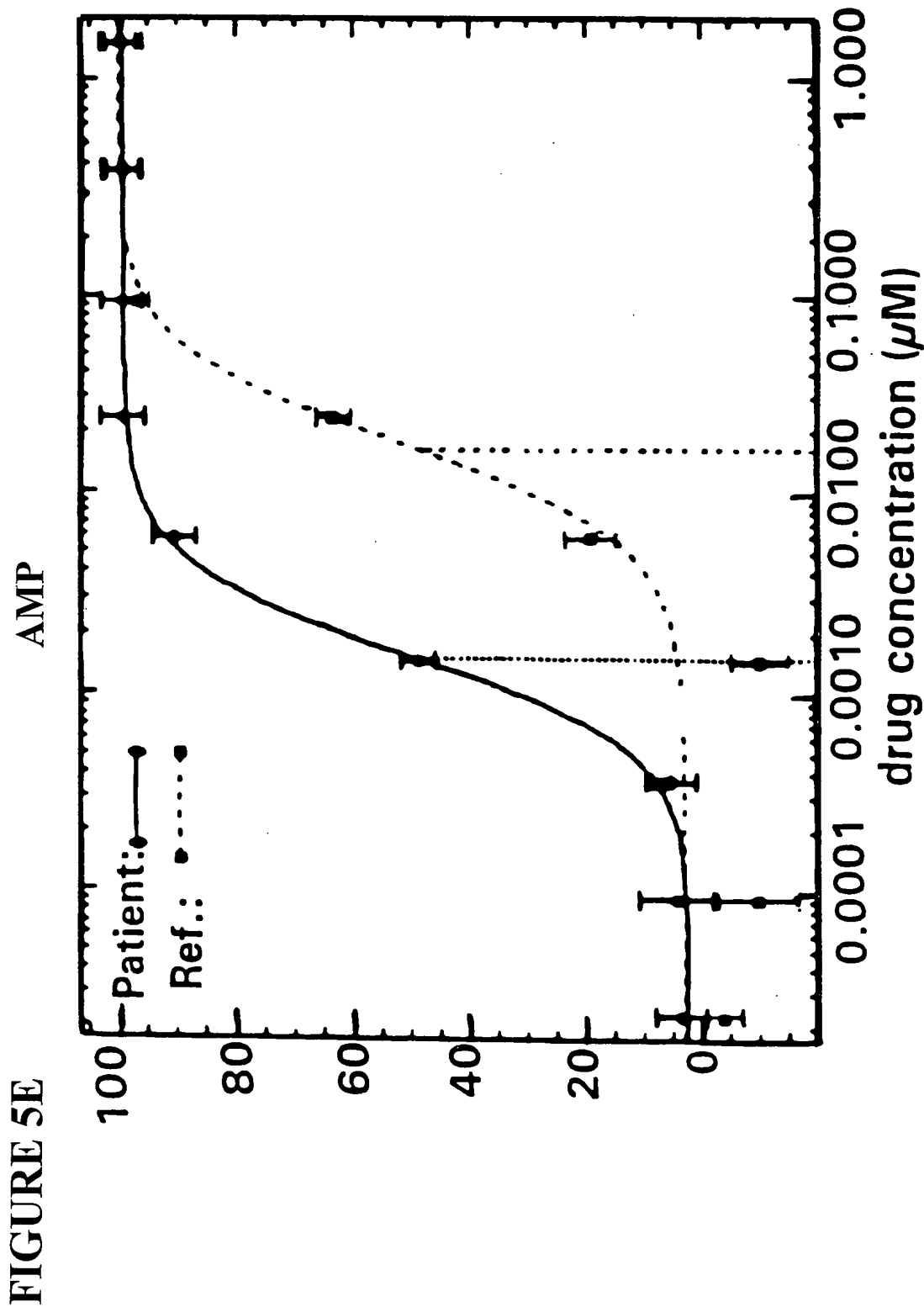
FIGURE 5D

NFV





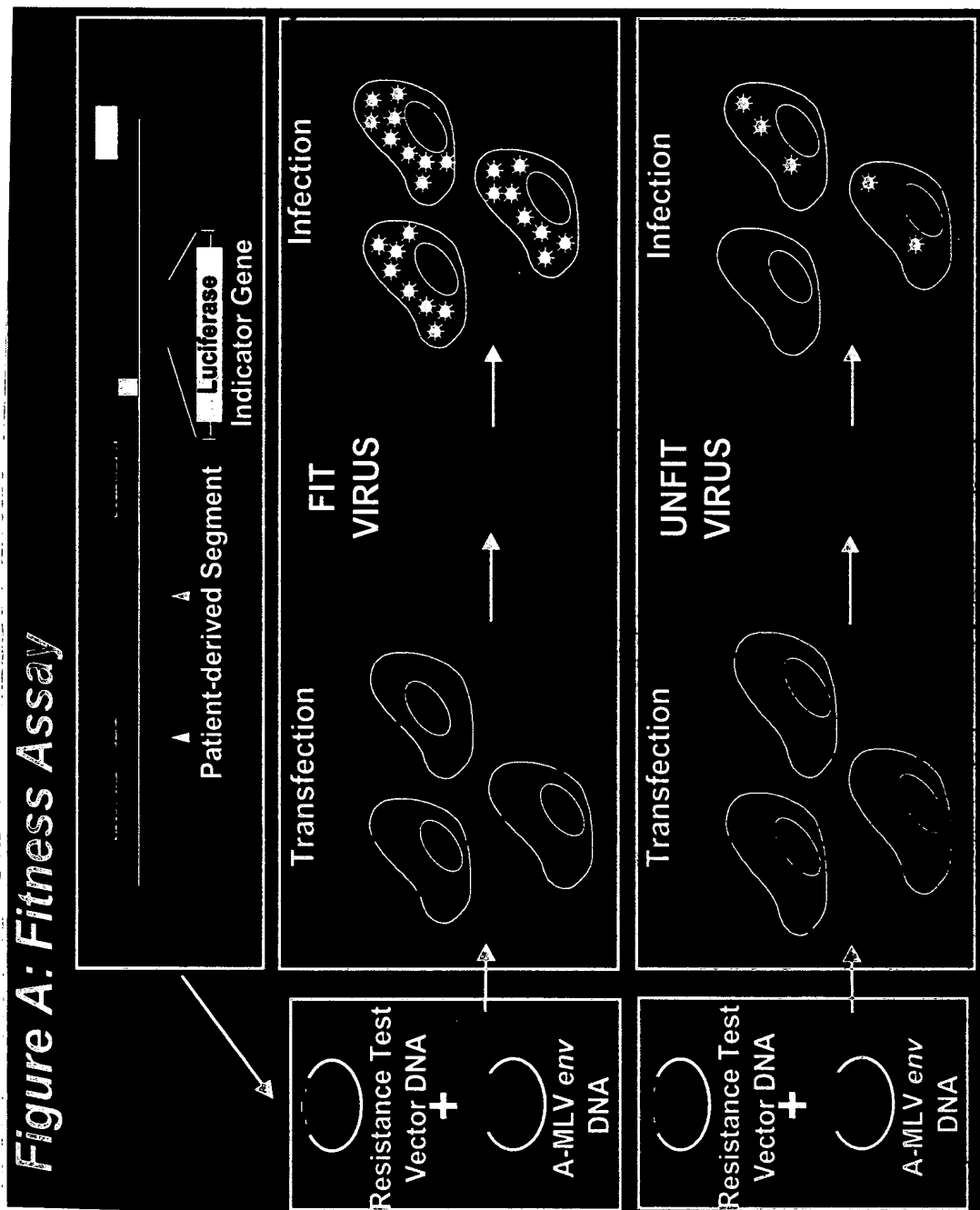
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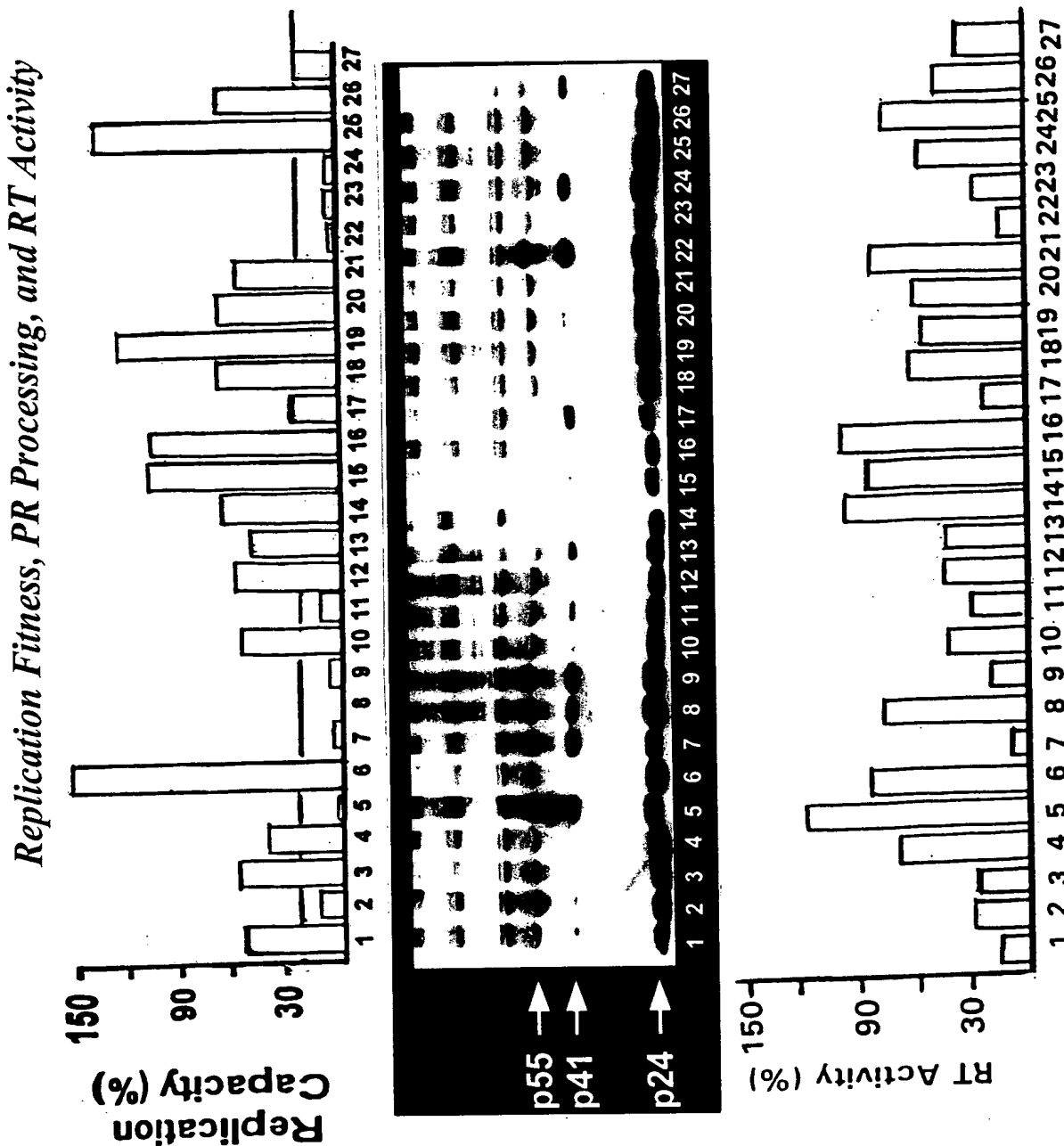
**FIGURE 6A**





60/LV/UV  
01d 'S'N 2960f

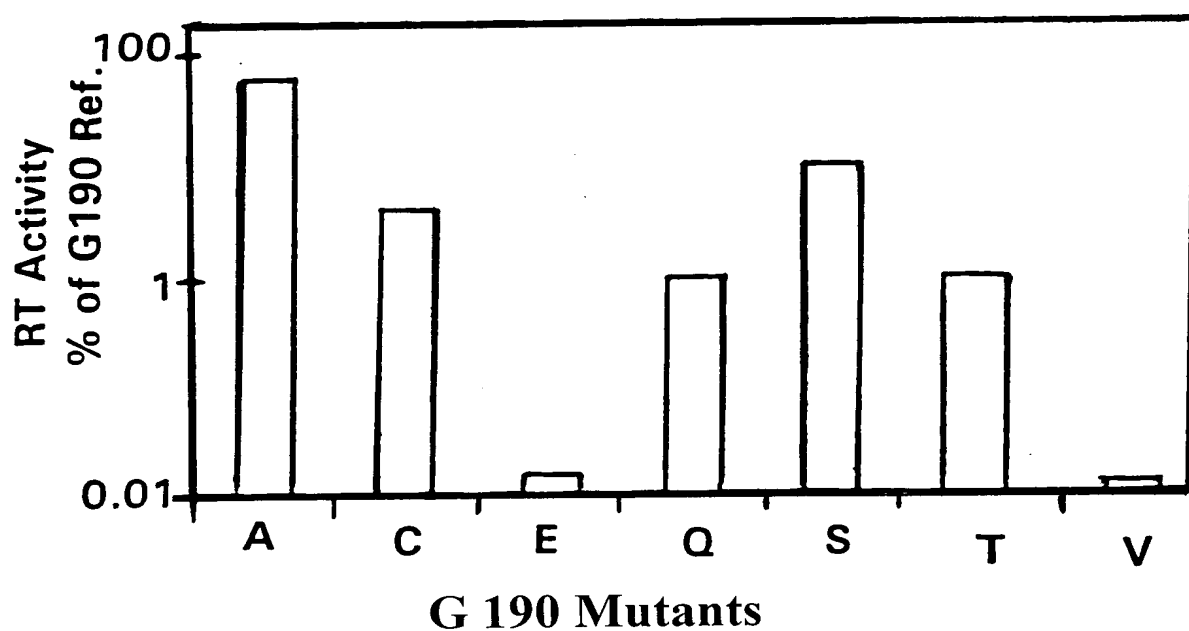
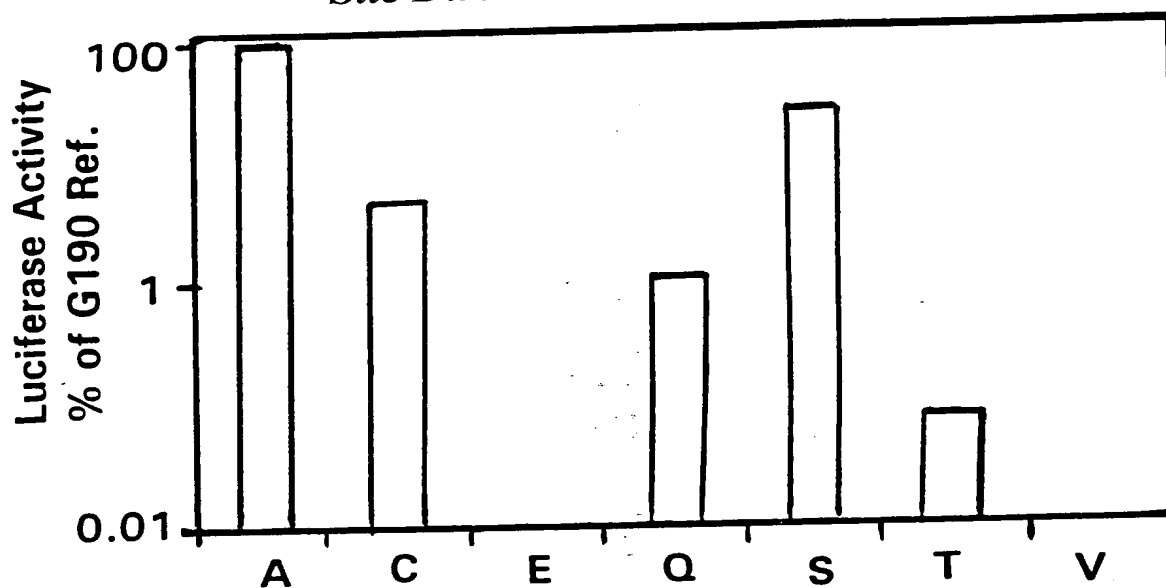
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FIGURE 6D

*Site Directed RT Mutants (G 190 Series)*



A = Ala      C = Cys  
E = Glu      Q = Gln  
S = Ser      T = Thr

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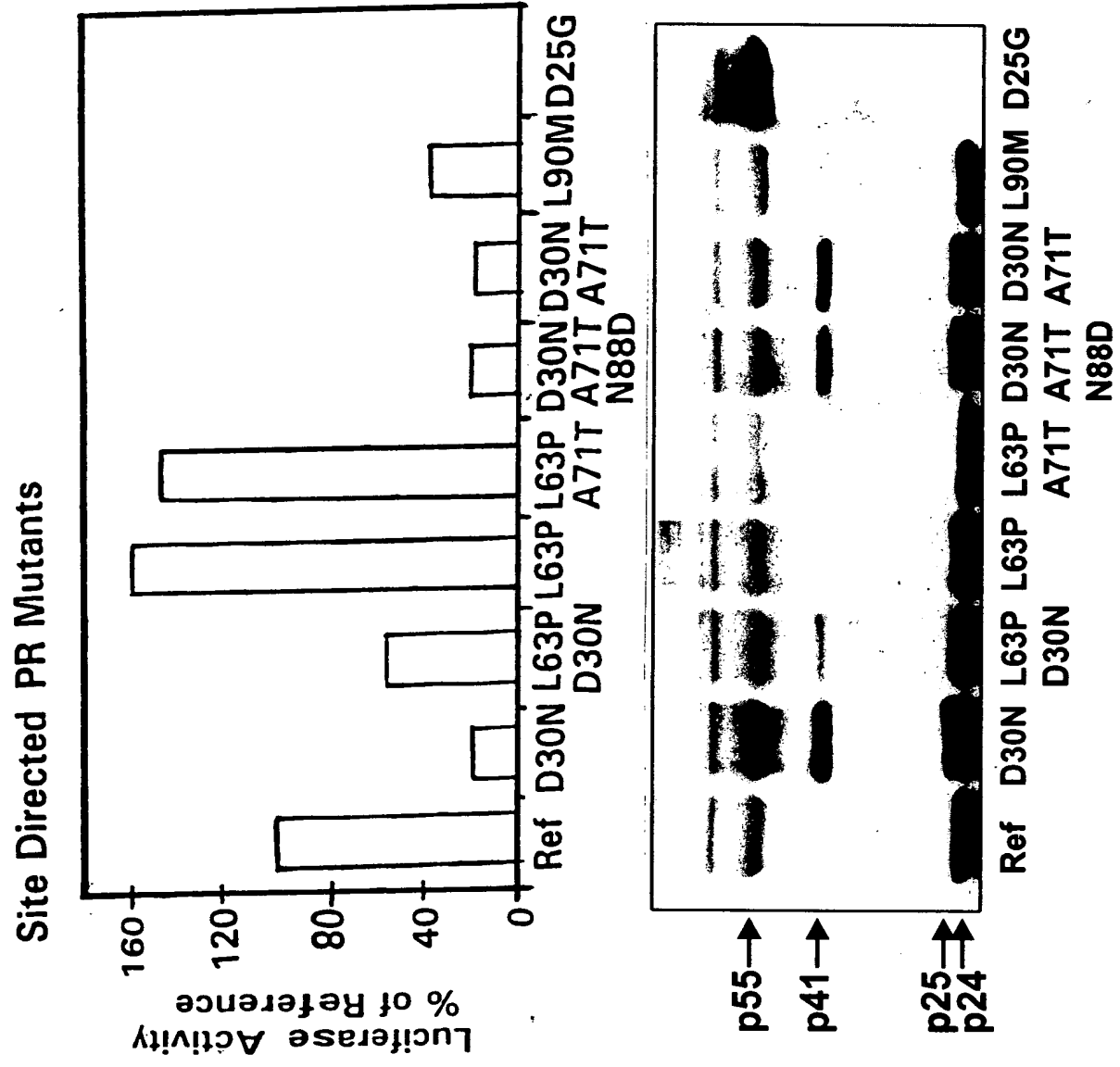


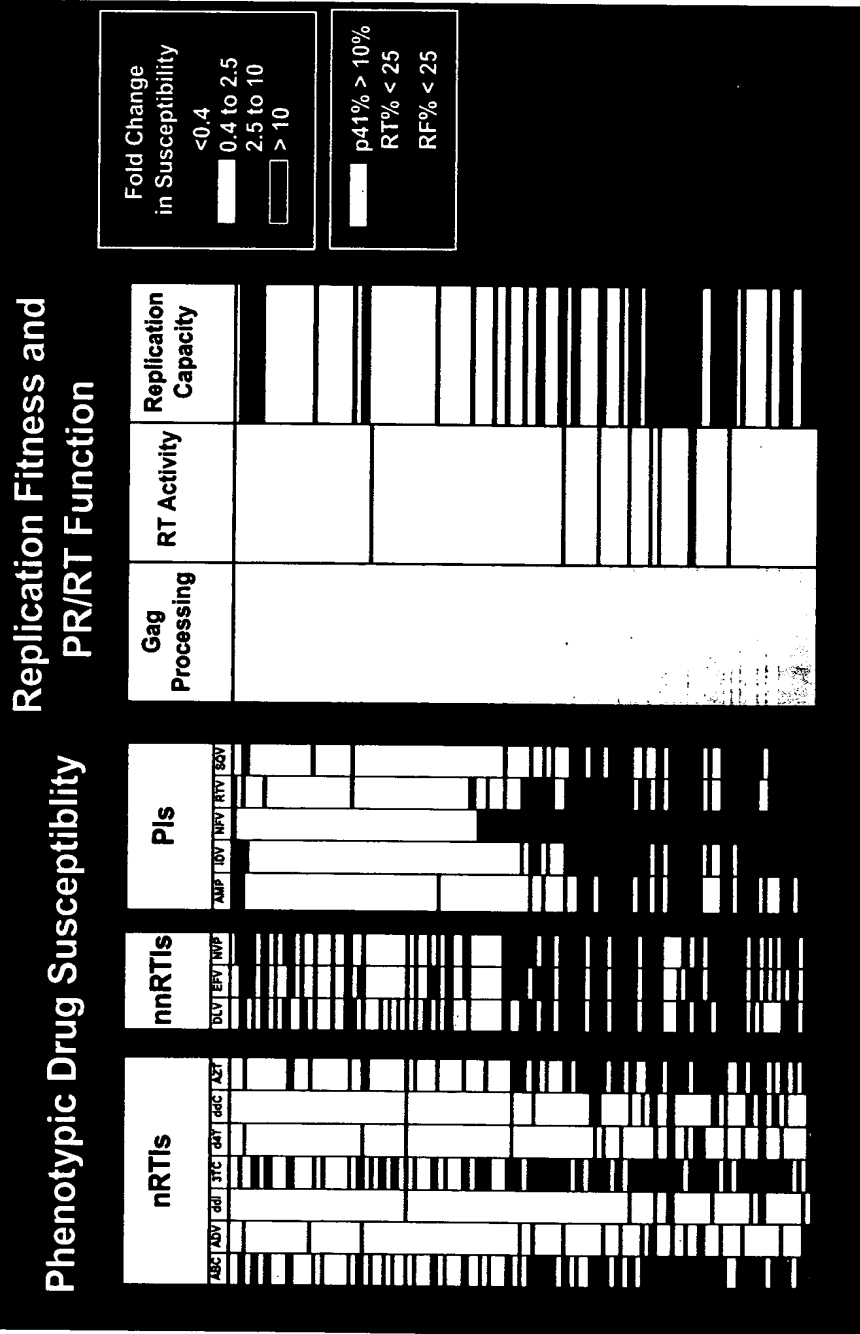
FIGURE 6E



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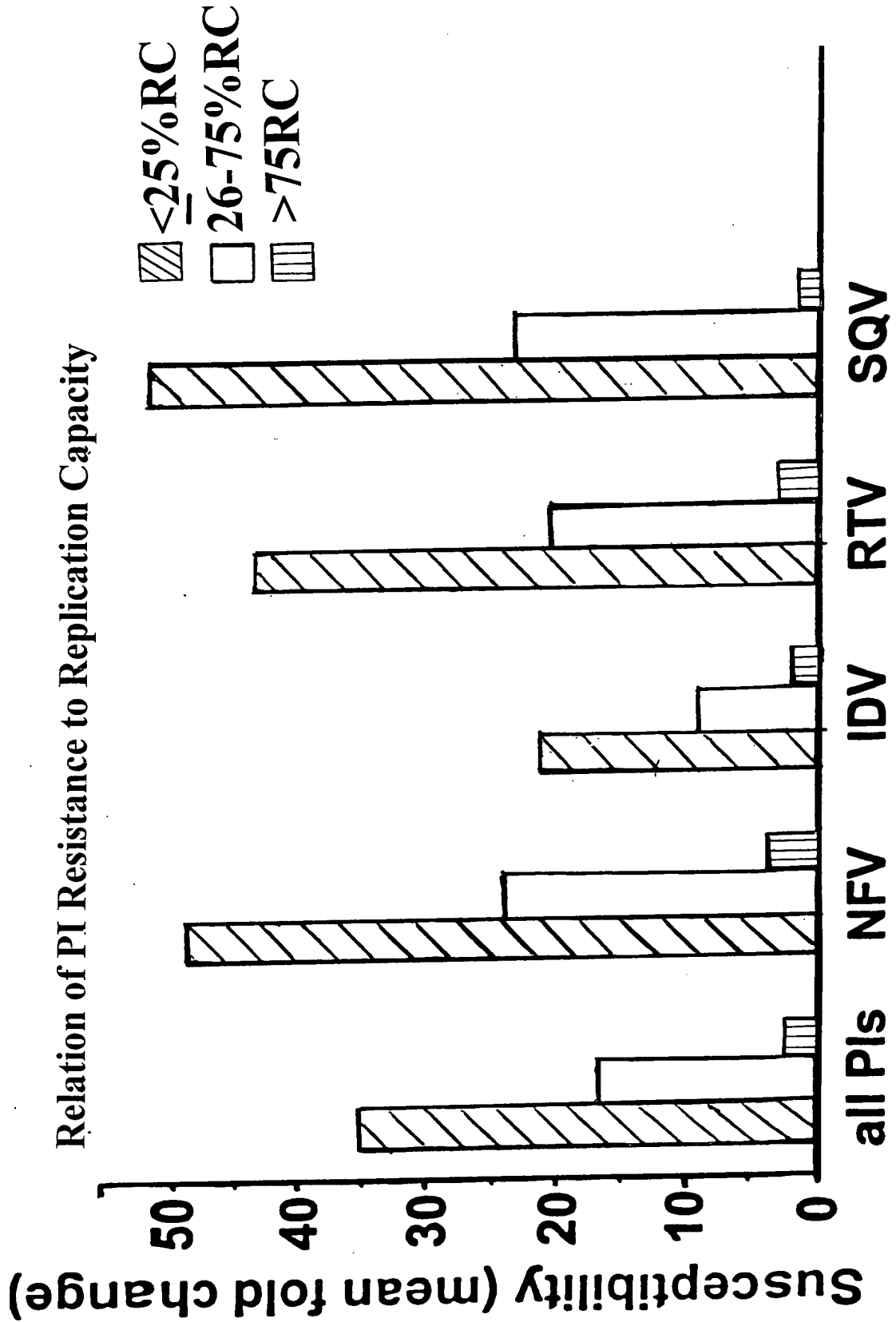
FIGURE 6F

*Figure F: Phenotypic Drug Susceptibility,  
Replication Fitness and PR/RT Function*



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FIGURE 6G





09874472 .101702

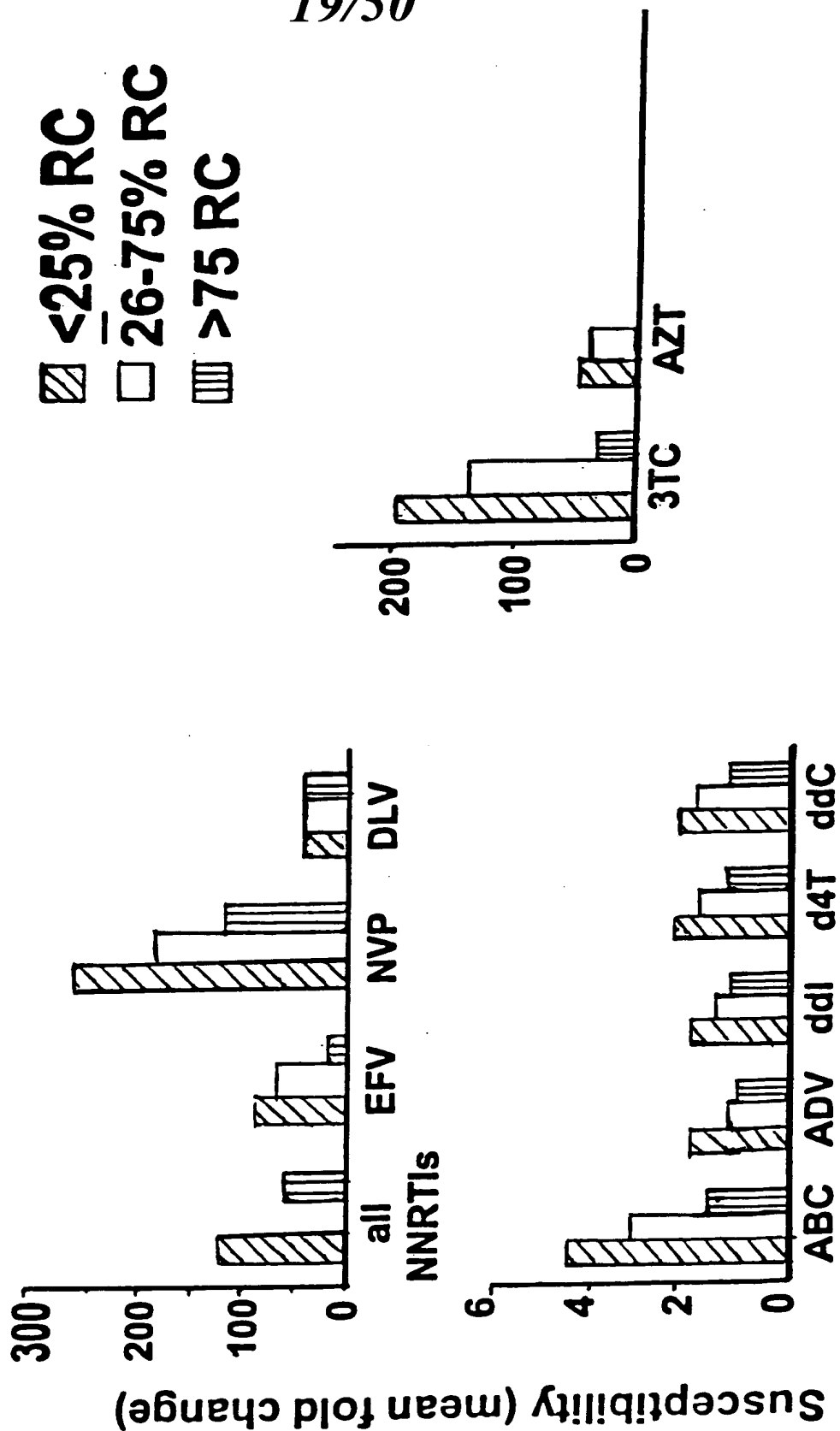
Applicants : Neil T. Parkin and Rainer Ziermann  
U. S. Serial No. 09/874,472  
Filing Date: June 4, 2001  
Title of the Invention: MEANS AND METHODS FOR  
MONITORING PROTEASE INHIBITOR  
ANTIRETROVIRAL THERAPY AND GUIDING  
THERAPEUTIC DECISIONS IN THE TREATMENT  
OF HIV/AIDS

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FIGURE 6H

Relation of NRTI and NNRTI Resistance to Replication Capacity

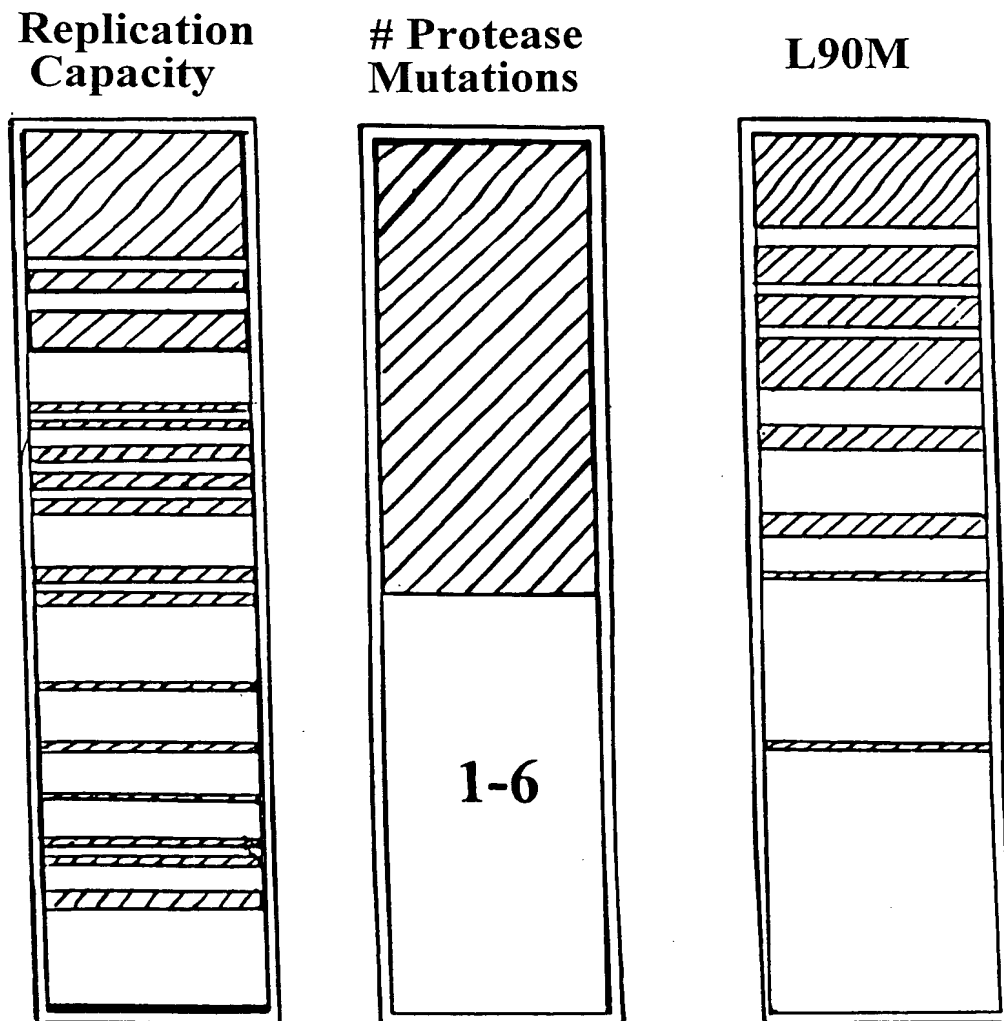




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## FIGURE 6I

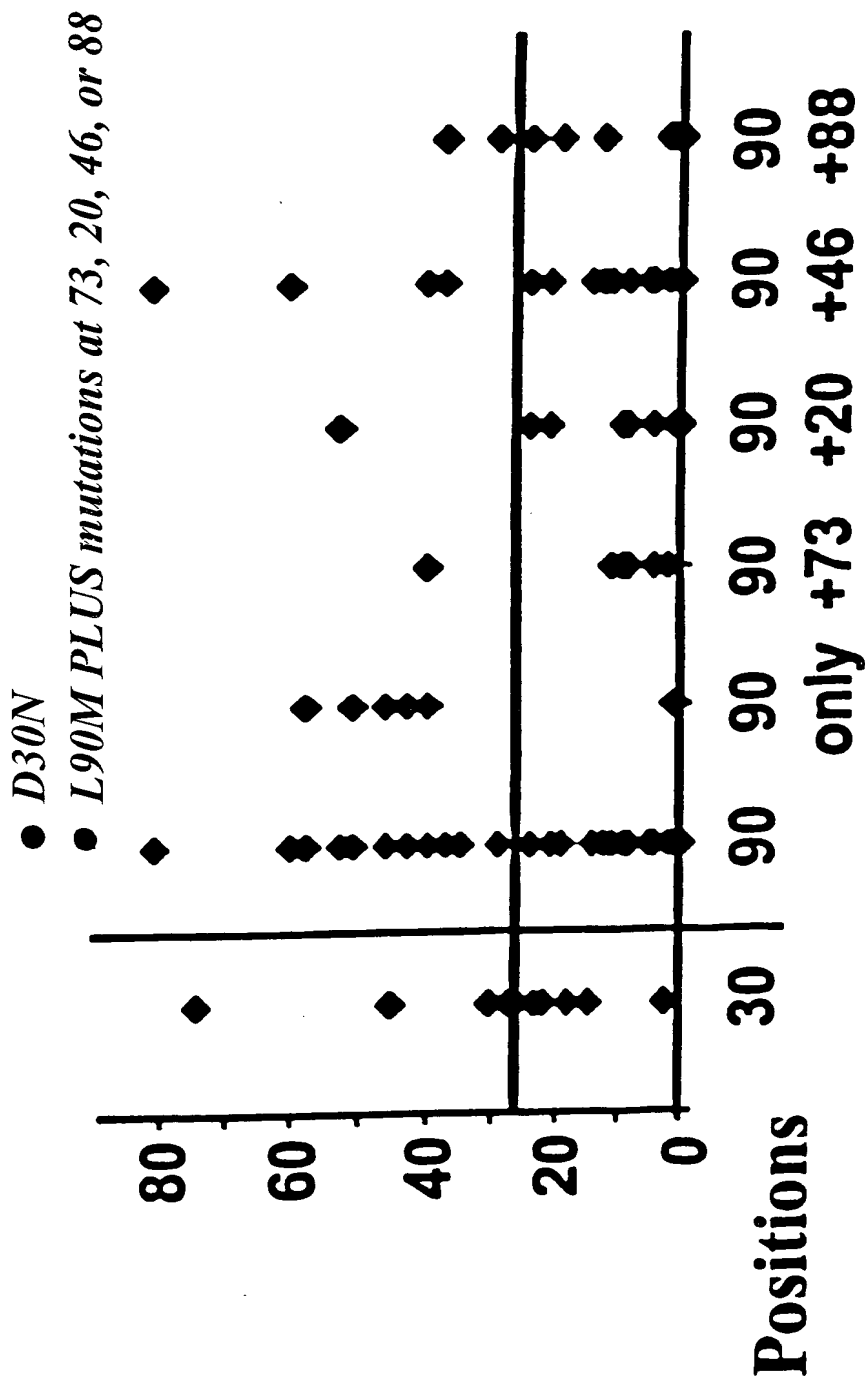
**Low Replication Capacity is Associated with High  
Numbers of Mutations in Protease and L90M**





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**FIGURE 6J**  
 Low Replication Capacity is Associated With Specific  
 Protease Mutations



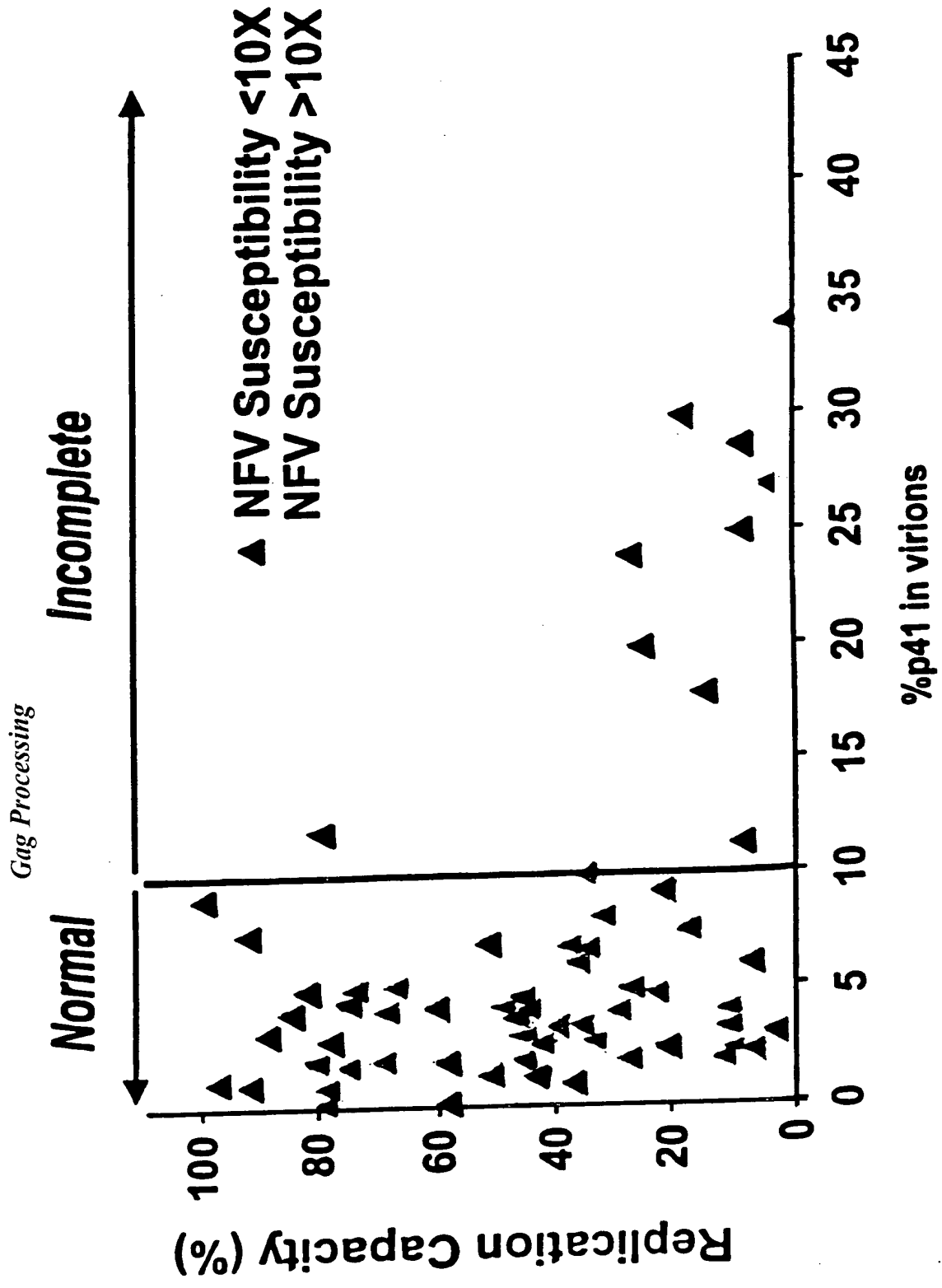
p value .05 <.05 <.01 <.01 .06



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Relation of NFV Phenotypic Drug Susceptibility, gag Processing and  
Replication Fitness

FIGURE 6K



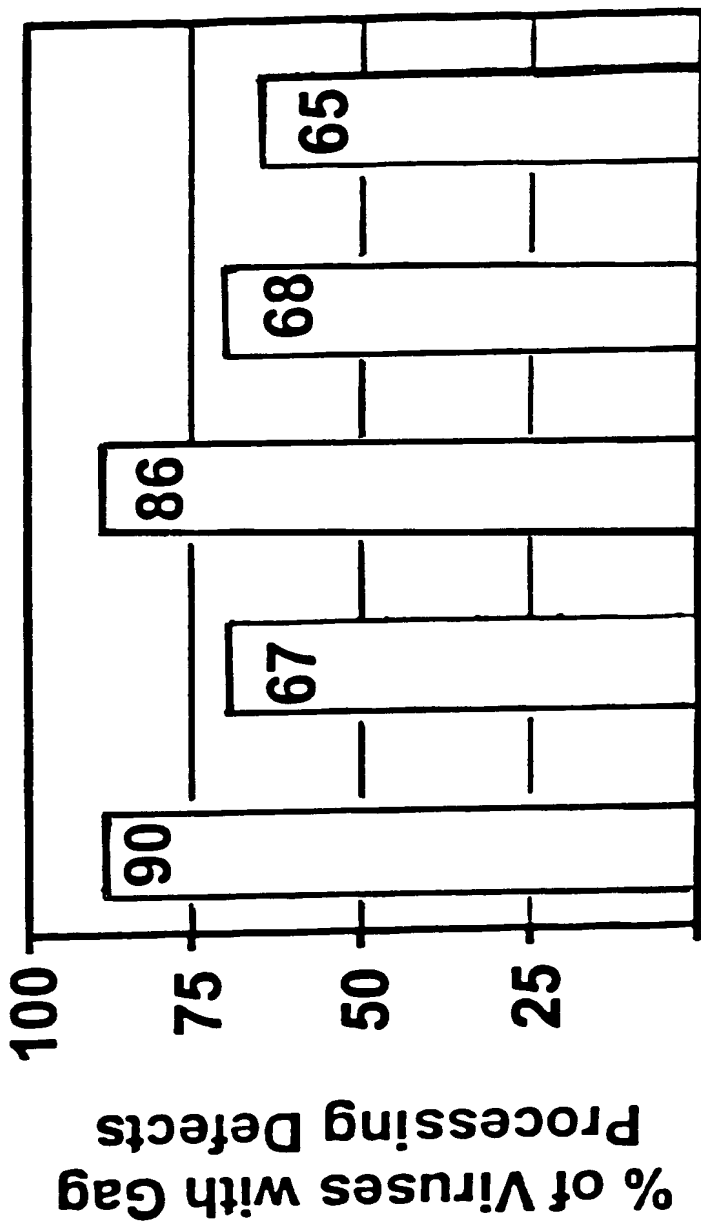


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*Mutations in PR Associated with Gag Processing Defects*

**FIGURE 6L**

**D30N** **M46I/L** **G48V** **154L/A/S/T/V** **184V**



**Position**

**p value** <0.1% <0.1% <1% <0.1% <1%

**n**

**10** **24** **7** **19** **17**



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FIGURE 6M

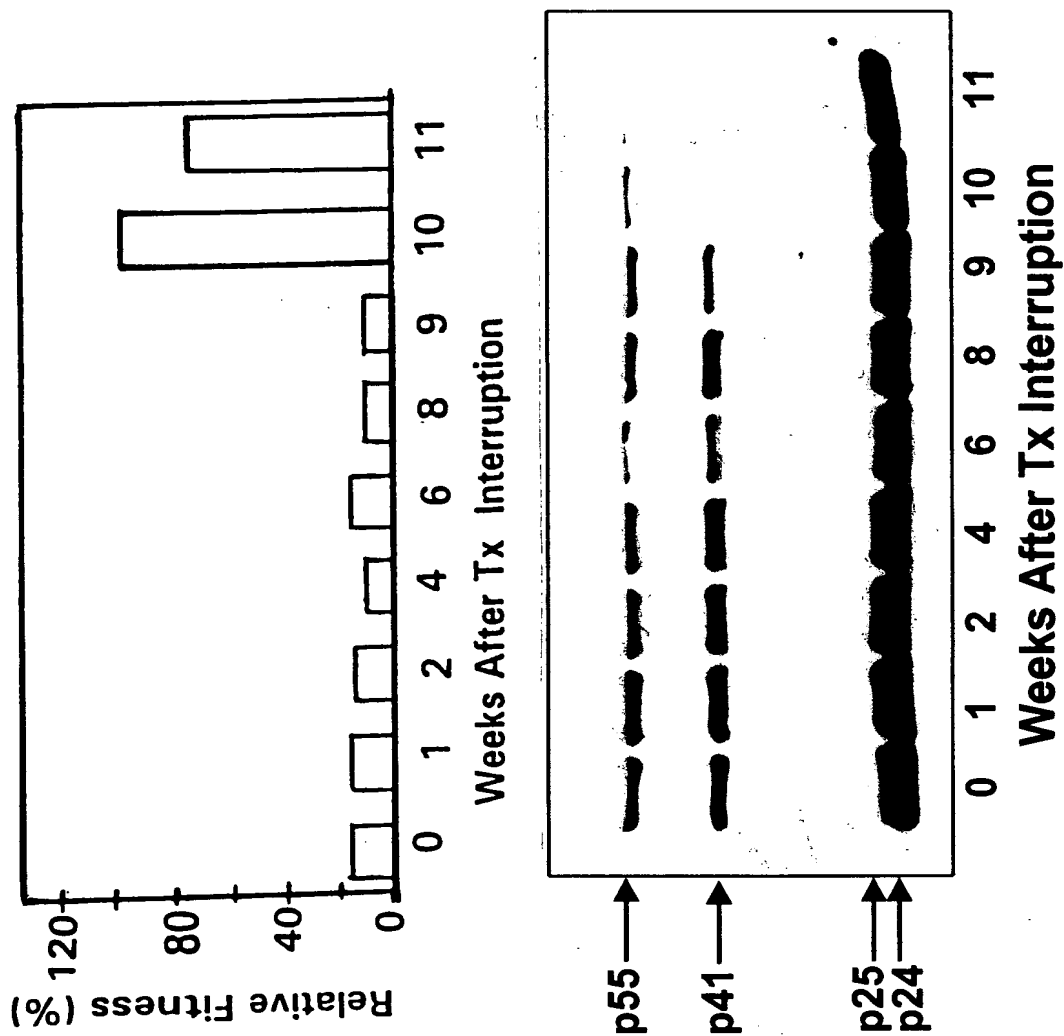
PI												
NNRTI												
NRTI												
WEEK	AZT	3TC	D4T	ABC	NVP	DLV	EFV	SQV	IDV	RTV	NFV	AMP
day 0	3.7	>100	2.8	19	>300	88	115	85	72	73	74	16
1	4.5	>100	3.3	20	>300	78	134	95	74	59	80	21
2	5.8	>100	3.2	14	>300	75	142	89	77	49	59	19
3	6.5	>100	2.7	15	>300	96	183	59	75	52	51	15
4	6.3	>100	3.1	15	>300	94	174	59	68	50	49	15
5	6.4	>100	3.0	17	>300	76	119	59	60	54	36	10
6	5.0	>100	2.8	19	>300	93	168	89	39	80	40	18
7	9.1	>100	4.1	12	>300	89	154	85	78	53	53	19
9	2.8	8.1	1.9	5.0	22	15	10	1.8	3.5	4.7	4.0	2.0
10	1.5	1.7	1.1	1.3	1.7	2.0	1.6	0.9	1.6	1.9	1.8	1.6
11	0.9	1.2	1.0	1.2	0.8	1.1	0.9	1.0	1.1	1.1	1.1	1.0
12	0.8	1.3	0.8	1.2	0.5	1.0	0.8	0.8	0.8	0.9	1.1	0.8
23	0.7	1.1	1.0	0.6	0.8	1.1	0.8	0.8	0.8	1.0	0.9	0.6

*Patient Virus Reversion to Drug Susceptibility After Treatment Interruption*



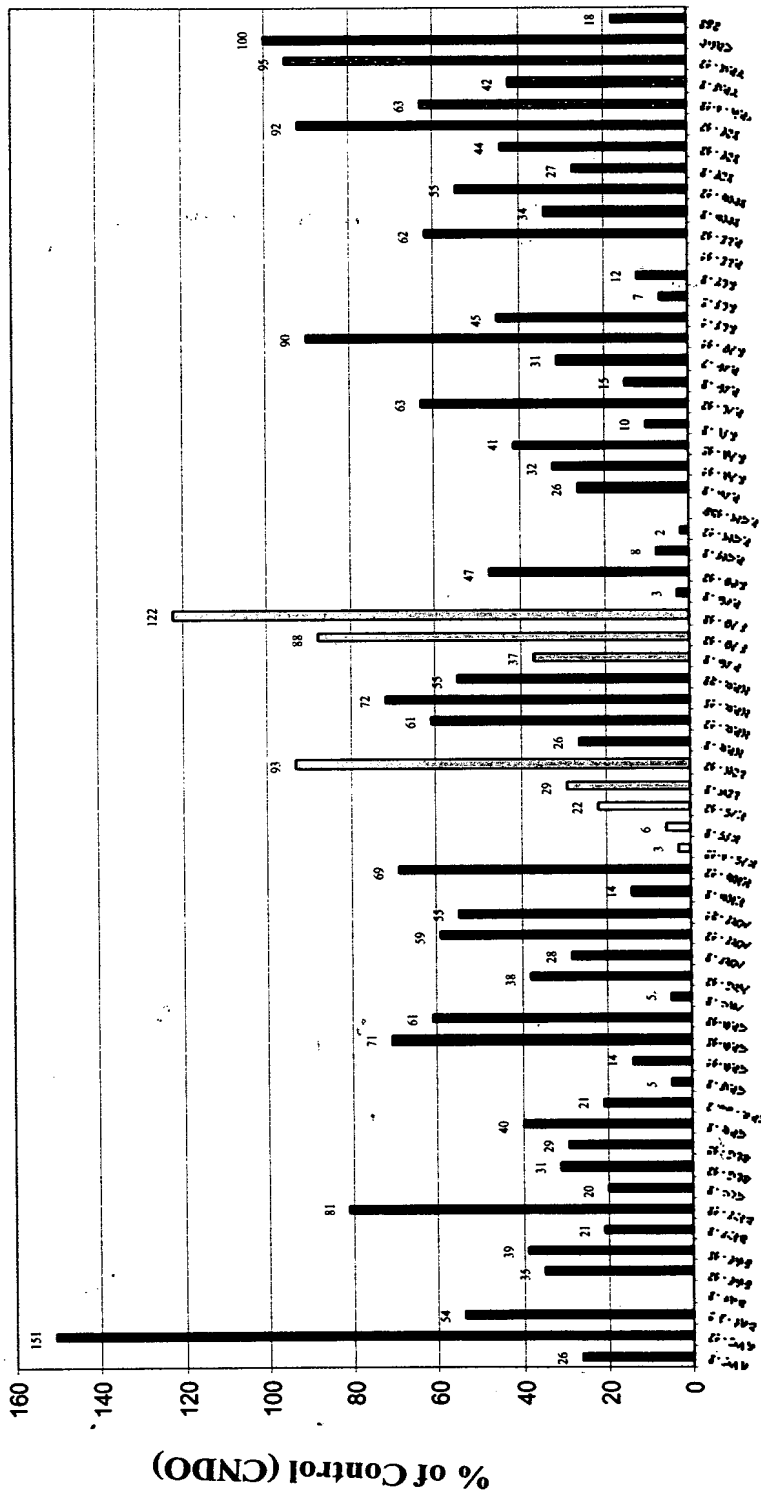
FIGURE 6N

Patient Virus Reversion to Normal Replication Fitness after  
 Treatment Interruption

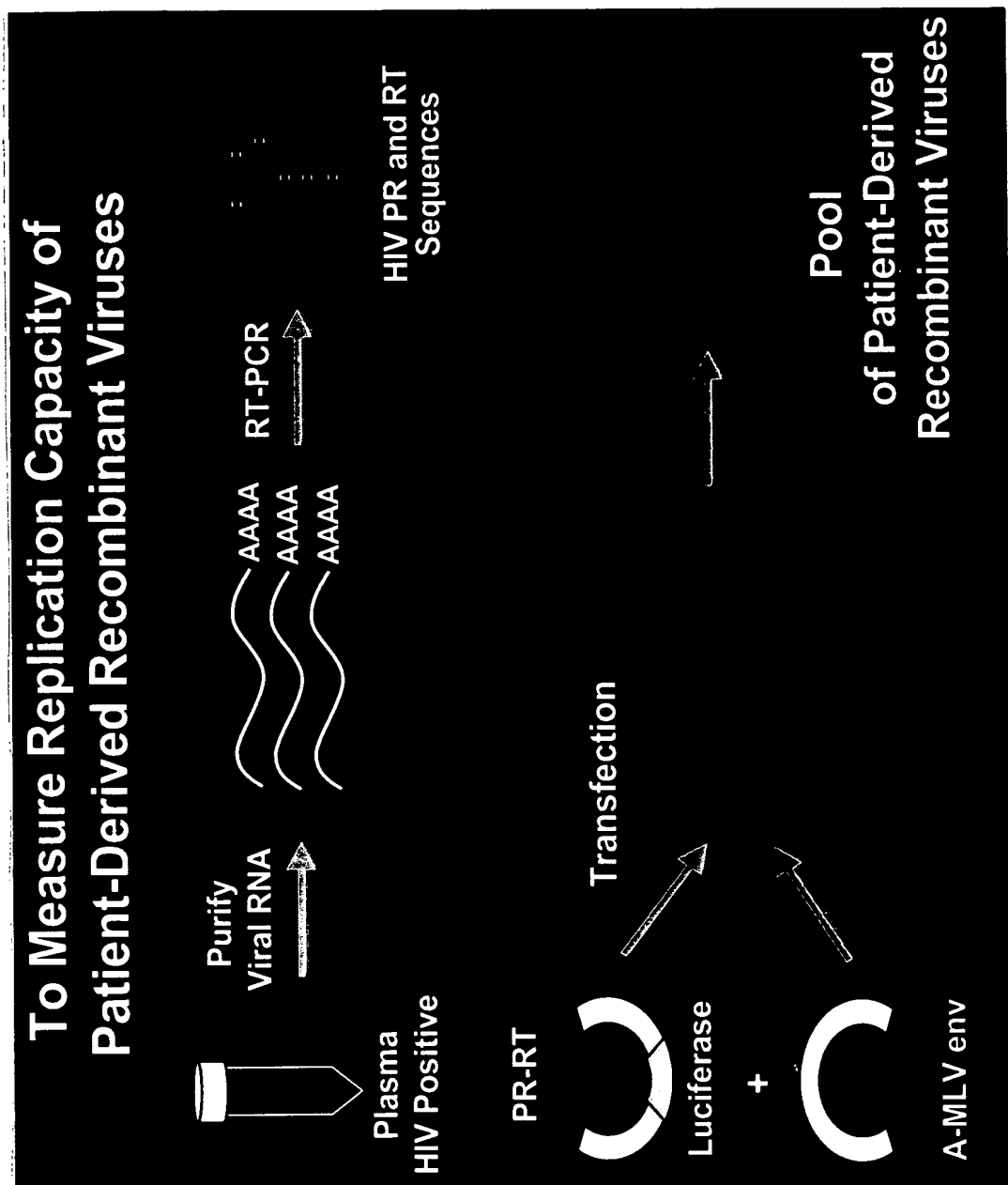


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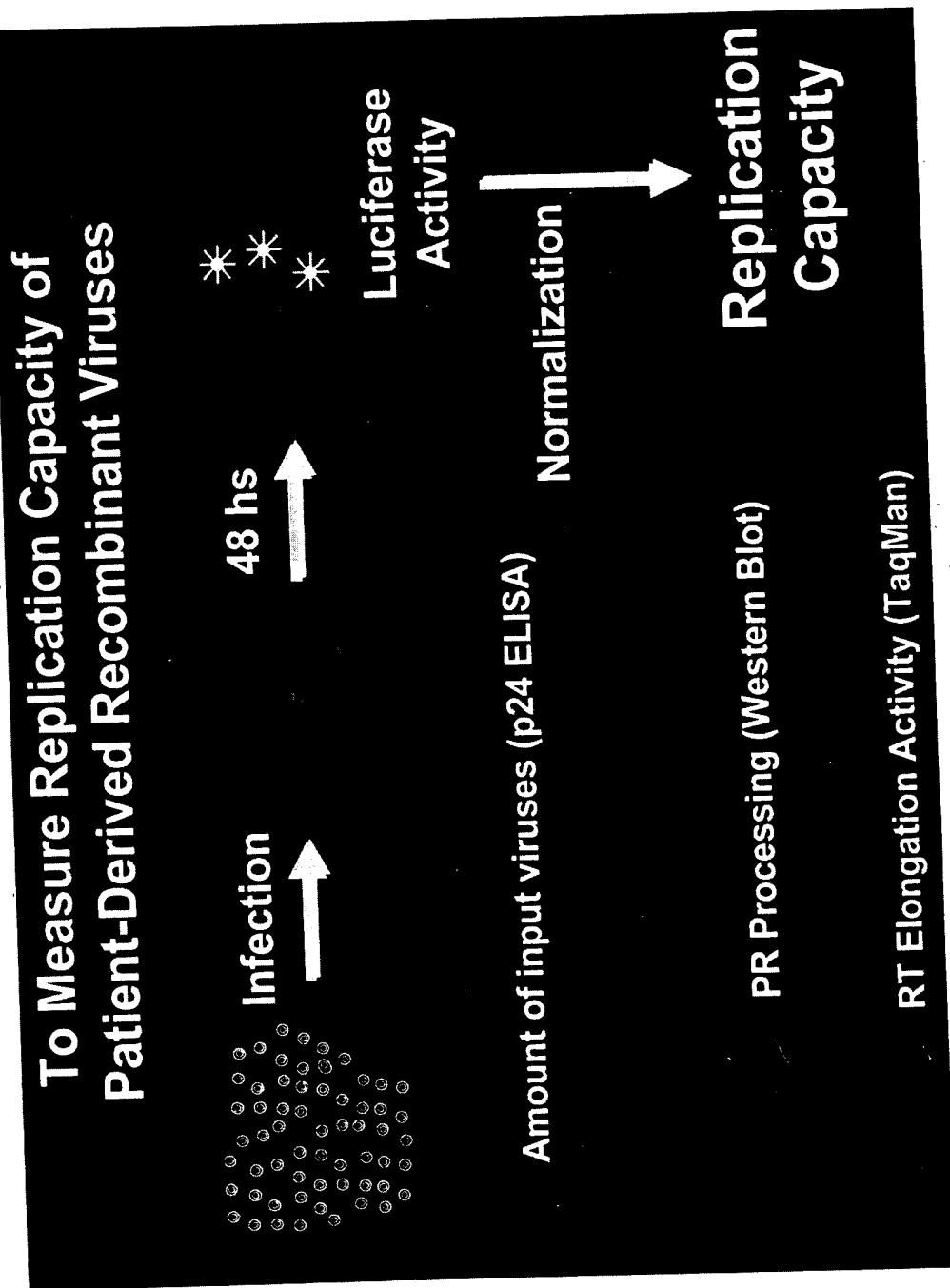
**FIGURE 60**  
Fitness on GCRC STI Samples (wk 0 and 12)-Assay#2  
RLU corrected for p24 input (% of control)



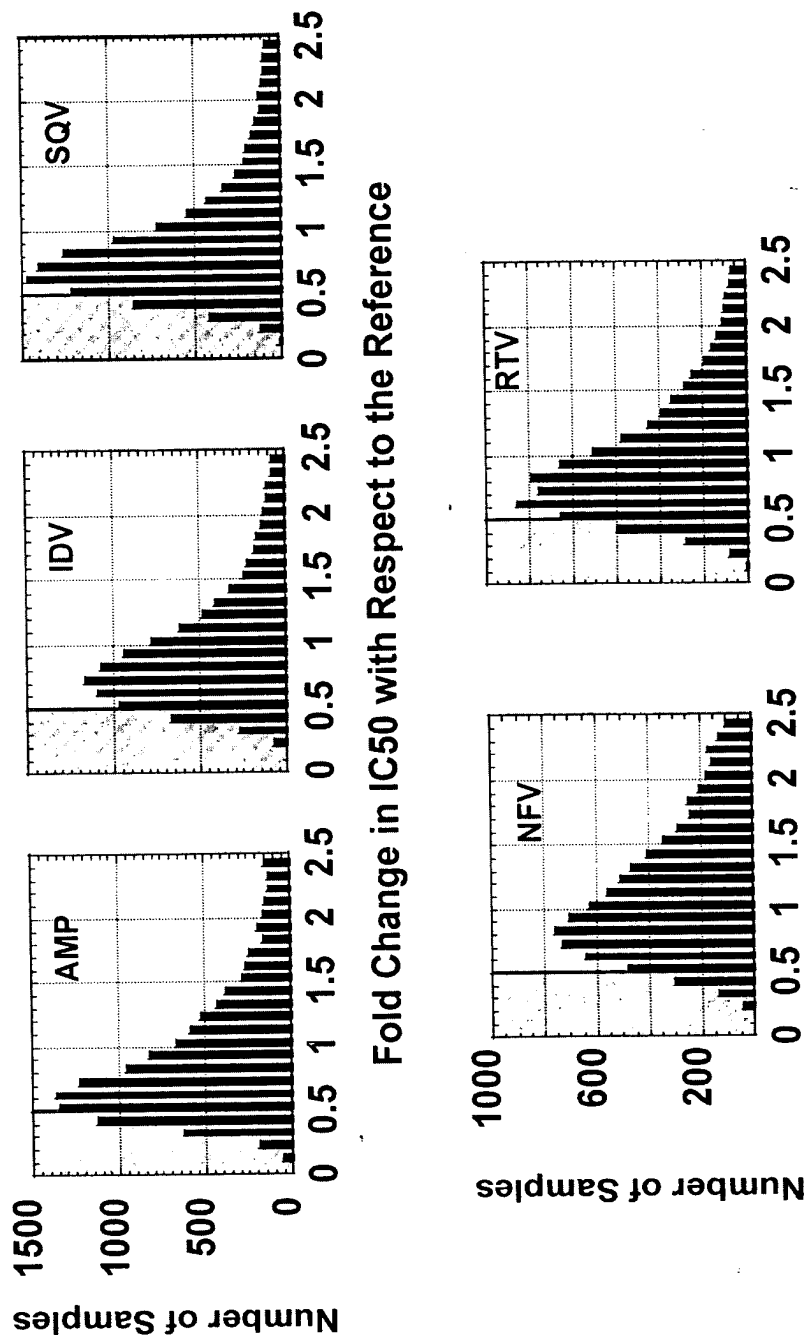
# FIGURE 6P



**FIGURE 6Q**



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**Fold Change in IC50 with Respect to the Reference**

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FIGURE 7

Fold Change Susceptibility  
20 Randomly Selected Patient Viruses with HS to PIs

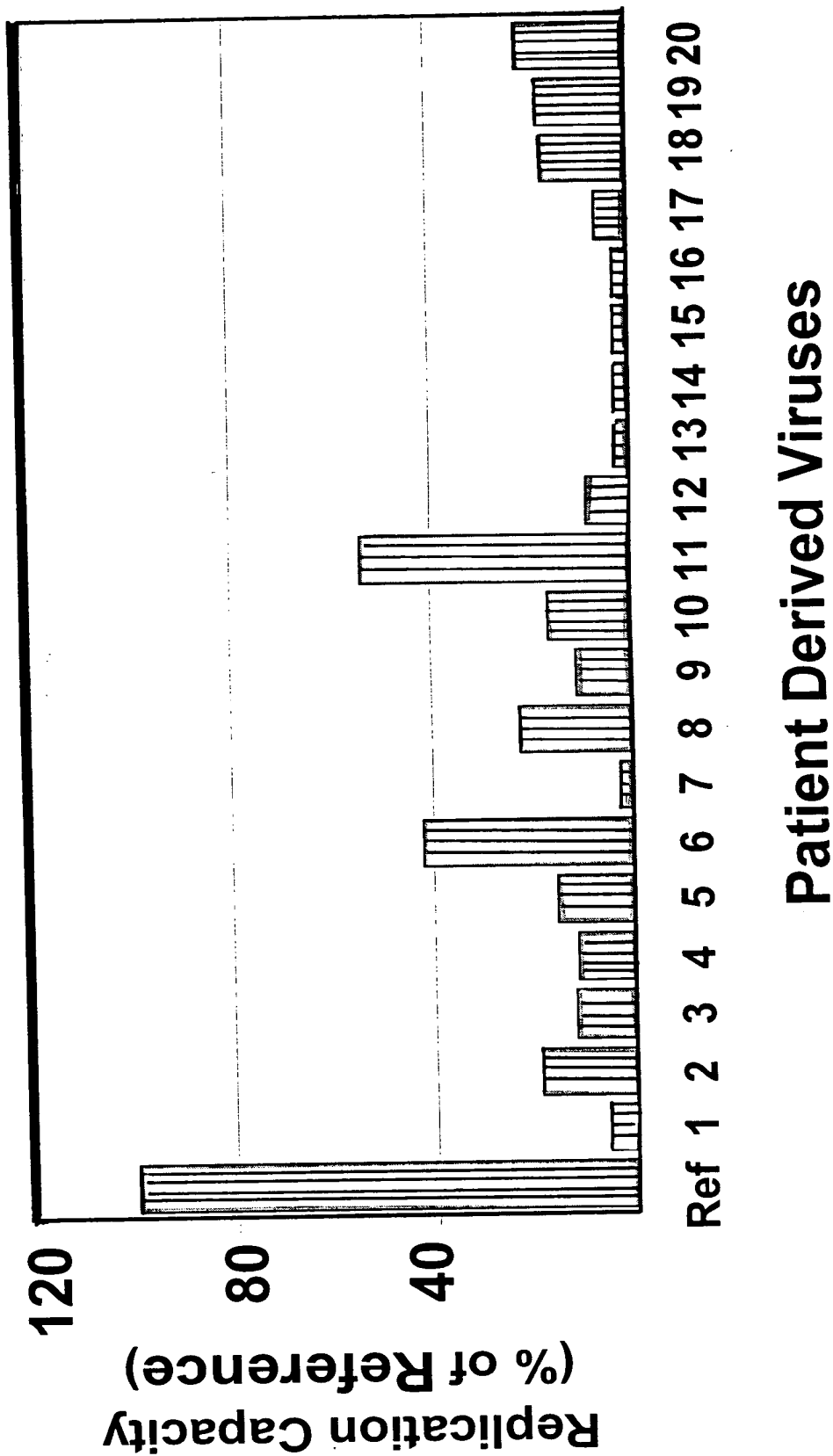
Sample	RT Inhibitors										PR Inhibitors									
	ABC	ddI	3TC	d4T	ddC	ZDV	DLV	EFV	NVP	AMP	IDV	NFV	RTV	SQV						
1	3.2	2.2	>300	0.9	1.7	1.2	0.9	41.9	>700	0.4	0.6	1.1	0.4	0.3						
2	1.0	1.0	1.3	1.1	1.1	0.7	1.2	0.8	0.8	0.6	0.3	0.7	0.2	0.3						
3	3.1	1.7	>300	0.9	nd	0.7	nd	1.1	0.8	0.2	0.4	0.6	0.4	0.3						
4	3.3	1.9	>300	1.0	2.4	1.2	62.9	101	429	0.2	0.4	0.6	0.4	0.2						
5	3.5	2.2	5.0	1.7	3.2	0.6	>190	>320	>700	0.2	0.4	0.6	0.5	0.3						
6	7.5	1.4	>300	1.4	2.1	22.9	12.8	135	>700	0.5	0.5	0.6	0.4	0.4						
7	3.5	1.9	>300	3.7	3.4	73.9	30.6	>320	>700	0.3	0.4	0.6	0.3	0.4						
8	2.7	1.6	>300	1.0	1.8	1.1	>190	89.3	>700	0.4	0.4	0.5	0.6	0.4						
9	2.0	1.1	>300	0.7	1.3	0.8	6.9	72.1	165	0.3	0.4	0.5	0.3	0.5						
10	2.4	1.7	>300	1.2	1.9	0.6	71.5	38.7	109	0.4	0.4	0.4	0.4	0.4						
11	2.6	1.5	>300	0.7	1.7	0.4	30.9	94.9	193	0.4	0.4	0.4	0.5	0.4						
12	3.4	1.1	>300	1.0	2.1	0.7	3.2	2.0	2.6	0.3	0.5	0.4	0.5	0.4						
13	3.1	2.1	>300	1.1	3.6	0.6	2.4	1.1	1.5	0.3	0.3	0.4	0.3	0.3						
14	1.6	1.1	2.0	0.9	1.5	0.9	>190	60.4	>700	0.2	0.3	0.3	0.2	0.2						
15	1.2	1.0	1.2	1.1	1.2	1.7	1.2	1.2	1.2	0.2	0.4	0.3	0.4	0.6						
16	2.8	1.3	3.5	1.2	1.2	14.3	21.9	12.4	71.8	0.2	0.3	0.2	0.2	0.4						
17	3.0	2.0	>300	1.2	1.8	2.0	11.3	22.1	160	0.2	0.2	0.2	0.2	0.2						
18	3.9	1.4	>300	1.6	1.5	3.1	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.3						
19	3.1	1.1	49.5	1.6	1.5	6.9	13.4	9.9	33.2	0.3	0.2	0.2	0.2	0.2						
20	0.9	1.2	1.3	0.9	0.8	1.0	0.8	0.6	0.6	0.3	0.3	0.2	0.3	0.3						

0 - 0.4      0.4 - 2.5      2.5 - 10      > 10

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jc962 U.S. PTO

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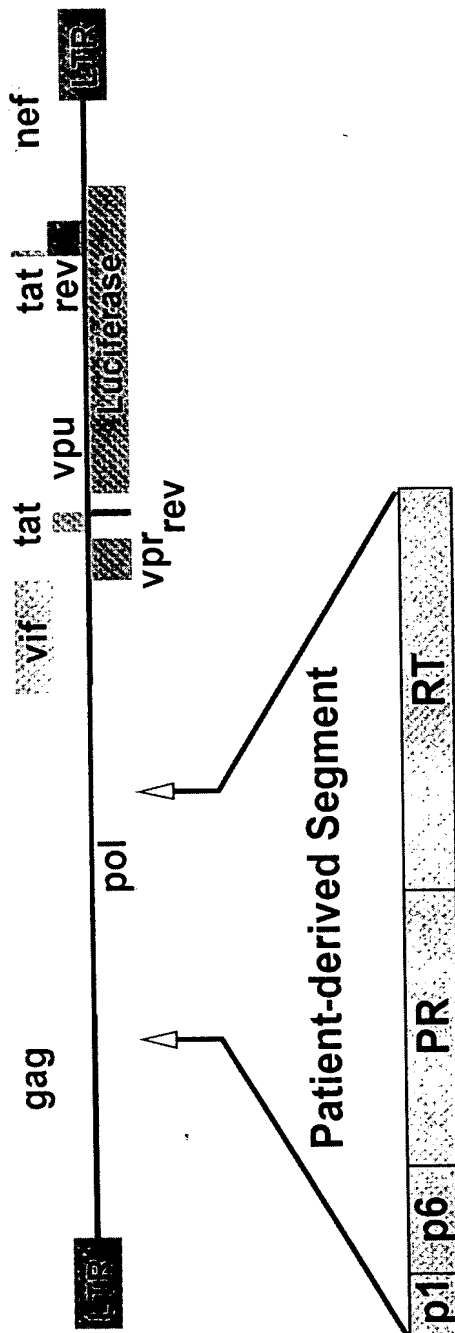
FIGURE 8



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**FIGURE 9**

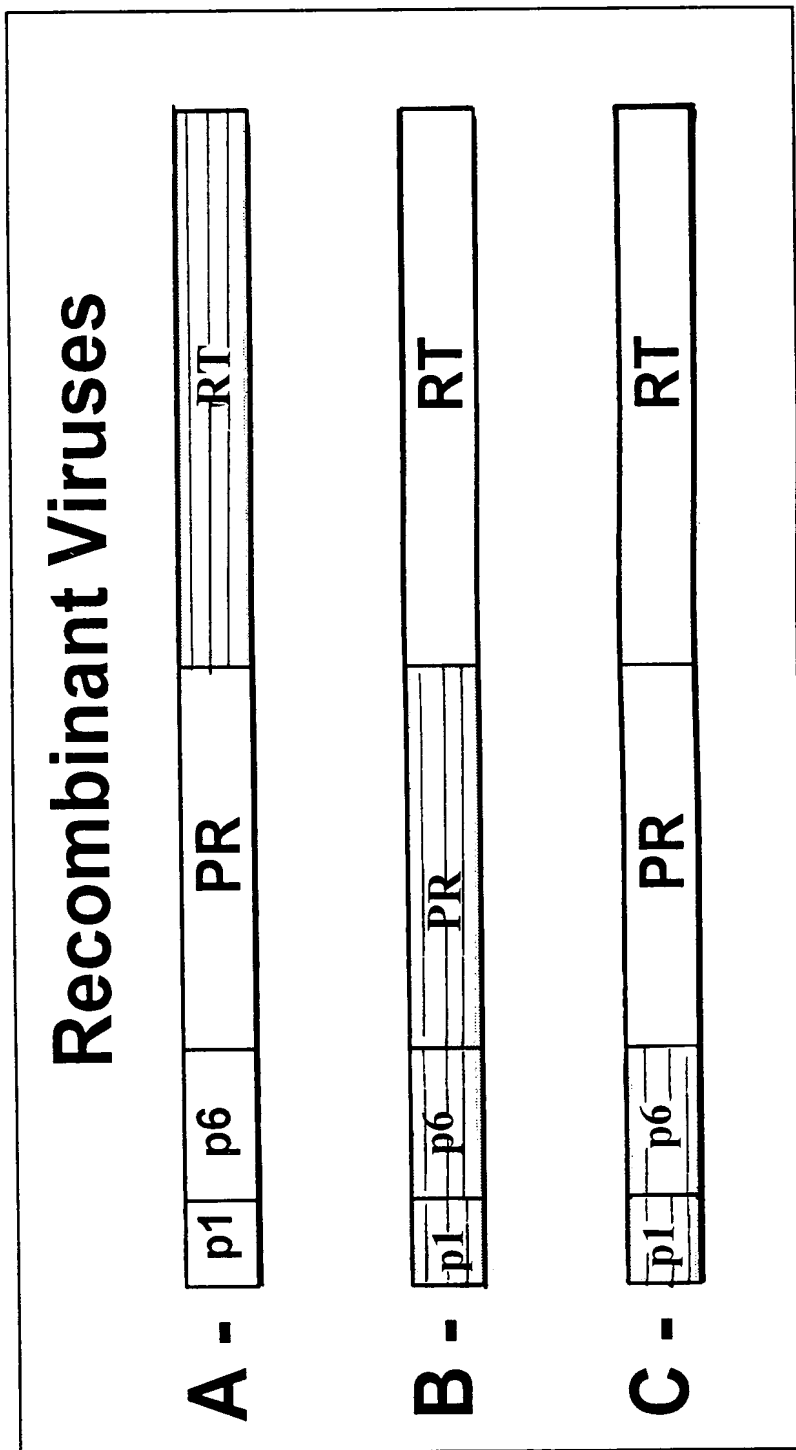
*Cell based assay to measure phenotypic drug susceptibility employing  
patient-derived recombinant viruses*





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FIGURE 10



NL4-3 Sequence  
 Patient Sequence

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FIGURE 11

A - p1 p6 PR RT  
NL4-3 Sequence Patient Sequence

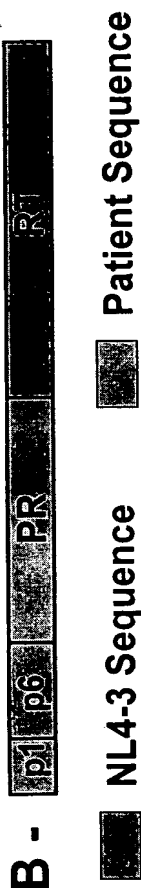
Fold Change in Susceptibility

Sample	ABC	ddl	3TC	d4T	ddC	ZDV	DLV	EFV	NVP	AMP	IDV	NFV	RTV	SQV
1	2.5	1.5	>300	0.8	1.5	0.8	0.7	35.8	>700	0.7	1.0	1.1	0.9	0.9
2	1.0	1.2	1.4	1.0	1.1	0.7	1.5	0.8	0.8	0.7	0.8	1.0	0.9	0.8
3	4.4	1.8	>300	0.9	2.1	0.7	2.1	1.1	1.4	0.6	0.9	0.9	0.7	0.4
4	3.5	1.8	>300	0.9	1.8	1.1	85.9	141	344	0.6	0.8	0.9	0.8	0.8
5	2.7	2.1	8.9	1.4	3.1	0.5	>190	>320	>700	0.5	1.0	1.1	0.7	1.0
6	7.0	1.4	>300	1.5	2.6	9.8	5.8	189	>700	0.7	0.5	0.8	0.7	0.7
7	9.9	2.6	>300	3.3	3.0	80.1	48.1	>320	>700	0.7	0.8	0.9	0.8	0.5
8														
9	1.9	1.1	>300	1.2	1.1	1.1	31.4	170	>700	0.7	0.7	1.4	0.8	0.9
10	3.8	1.8	>300	0.9	2.3	0.8	73.3	50	100	0.7	0.8	1.0	0.8	1.0
11	2.3	1.5	>300	0.7	1.7	0.5	35.6	130	182	0.6	1.1	1.0	1.0	0.8
12	4.3	1.9	>300	0.9	2.3	0.8	2.2	1.2	1.5	0.9	0.9	1.2	1.0	1.0
13	3.4	1.6	>300	1.0	2.1	0.4	2.1	0.8	1.2	0.8	1.0	1.0	1.0	1.0
14	5.7	1.8	>300	1.8	2.2	7.7	0.5	0.6	0.7	0.5	0.5	0.7	0.8	0.7
15	1.6	1.1	1.0	1.0	1.0	1.6	1.1	1.2	1.2	0.8	1.1	1.2	1.0	1.1
16	3.3	1.3	4.0	1.4	1.3	31	47.9	25	106	0.5	0.5	0.8	0.6	0.7
17	3.9	1.6	>300	0.8	2.0	2.2	12.6	33	166	0.5	0.8	0.7	0.9	0.7
18	5.7	1.8	>300	1.8	2.2	3.8	0.5	0.6	0.7	0.5	0.5	0.7	0.8	0.7
19	4.4	1.6	79.1	1.3	1.8	20	29	24	78	0.3	0.6	0.6	0.5	0.7
20	1.0	1.1	1.0	1.1	1.1	0.8	1.1	0.6	0.6	1.0	1.1	1.2	1.1	1.2

0 - 0.4 0.4 - 2.5 2.5 - 10 > 10

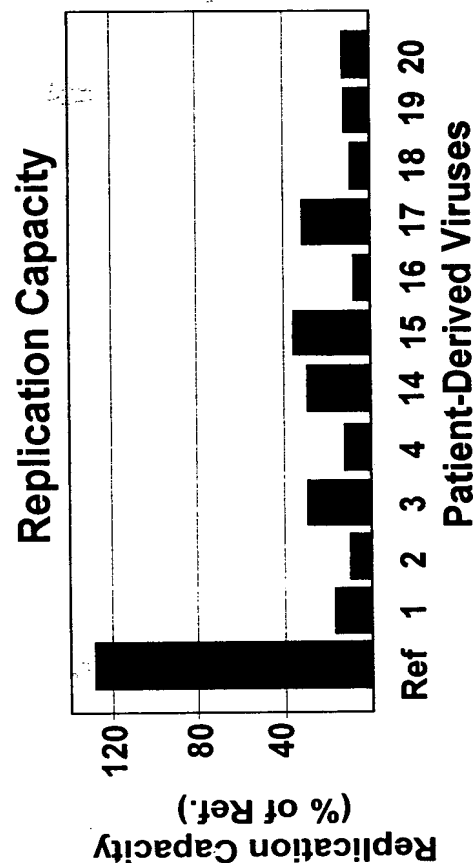
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FIGURE 12



Fold Change in Susceptibility

Sample	ABC	ddl	3TC	d4T	ddC	AZT	DLV	EFV	NVP	AMP	IDV	NFV	RTV	SQV
1	0.9	0.9	1.0	1.0	0.9	0.8	0.7	0.8	0.8	0.4	0.6	1.3	0.7	0.5
2	1.0	1.0	1.0	0.9	1.1	1.1	0.6	0.7	0.7	0.6	0.3	0.6	0.2	0.2
3	0.8	1.0	1.0	1.0	0.9	0.9	0.6	0.7	0.6	0.3	0.7	0.7	0.4	0.5
4	0.9	0.9	0.7	1.2	0.9	0.9	0.7	0.8	0.9	0.3	0.5	0.7	0.4	0.4
14	0.9	1.0	1.0	0.9	0.9	0.7	0.7	0.9	0.5	0.3	0.5	0.6	0.7	0.9
15	0.9	1.1	0.9	1.1	1.0	1.1	0.9	0.9	0.7	0.2	0.3	0.3	0.3	0.6
16	0.8	1.0	0.8	1.1	1.1	0.7	0.5	0.8	0.7	0.4	0.3	0.3	0.4	0.5
17	1.0	1.0	0.9	1.0	1.0	1.0	0.7	1.0	0.8	0.2	0.4	0.5	0.4	0.6
18	0.9	0.7	0.8	0.9	0.9	0.9	0.6	0.9	0.5	0.3	0.4	0.4	0.4	0.5
19	0.9	1.0	0.9	0.8	1.0	0.8	0.7	0.9	0.8	0.4	0.4	0.4	0.3	0.6
20	0.9	1.0	1.0	0.9	0.9	1.0	0.6	0.9	0.6	0.2	0.3	0.3	0.3	0.4



**FIGURE 13**



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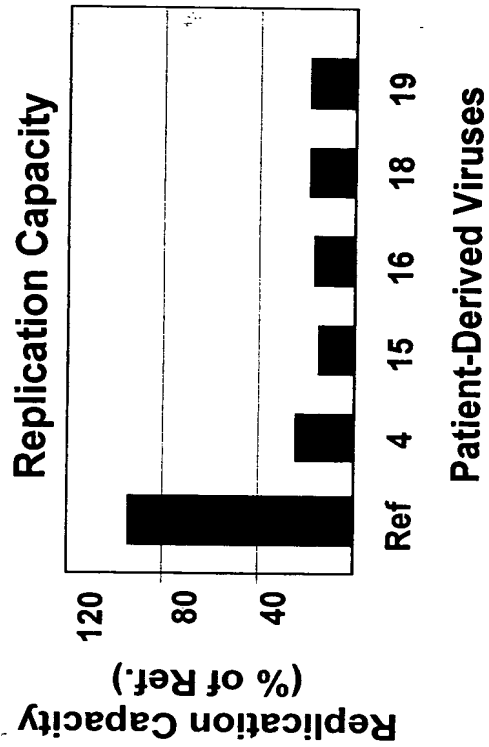
Age Group	Percentage of Respondents
18-29	~65%
30-49	~75%
50-69	~85%
70+	~90%

## NL4-3 Sequence

## Patient Sequence

## Fold Change in Susceptibility

Sample	ABC	ddl	3TC	d4T	ddC	ZDV	DLV	EFV	NVP	AMP	IDV	NFV	RTV	SQV
4	0.9	1.0	0.9	0.9	0.7	0.8	1.1	0.7	0.6	0.6	0.5	0.6	0.6	0.4
15	0.9	1.1	1.0	1.0	0.9	0.8	1.6	0.8	0.8	0.5	0.4	0.4	0.4	0.3
16	0.8	1.0	0.9	1.0	0.9	0.8	1.3	0.7	0.6	0.3	0.4	0.3	0.3	0.5
18	0.9	0.9	1.0	1.0	0.8	0.7	1.1	0.7	0.5	0.2	0.4	0.2	0.2	0.7
19	1.0	1.0	1.0	1.0	0.9	0.7	1.1	0.7	0.5	0.3	0.3	0.3	0.3	0.5



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**FIGURE 14**

**What Is the Role of Sequences Flanking  
the N-Terminus of PR?**

**1. The Gag Frame Encodes p1 and p6**

- p6 contains the L domain (PTAPP) which is critical for virus release from the cell
- p6 is required for proper incorporation of Vpr into the virions as well as retention of pol proteins
- p6 associates with TRiC (chaperonin)

**2. The Pol Frame Encodes a Transframe Protein (TFR)**

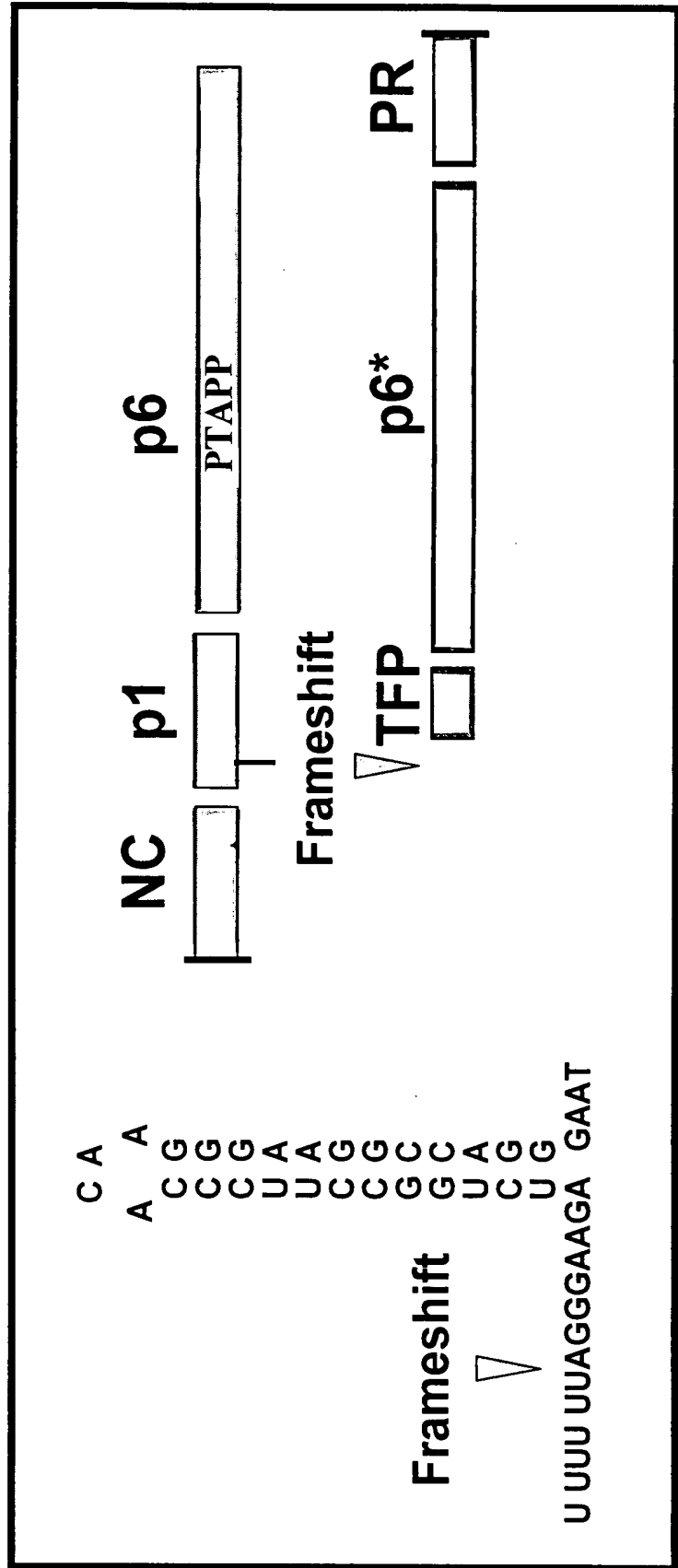
TFR includes a conserved octapeptide (TFP) and p6\*

- The TFP is a potent competitive inhibitor of PR in vitro
- p6\* modulates PR activity



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**FIGURE 15**  
*Contains Sequences and Structures Required for Frameshift  
 Slippery heptamer sequence (U UUU UUA)  
 Stem loop structure downstream of the frameshift site*





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**FIGURE 16**  
**Gag p1 and p6**  
*Genotype of Patient-Derived Sequences*

ANFLGKIWP SHKGRPGNF LQSRPEPTAPPEESFRFGEEETTPSQKQEPIDKELYPLASLRSLFGNDPSSQ

I	.....S.....N.....A.....G.....ST.....
II	.....V.....S...A.....T.....K.....L.....
III	.....L.....N.T.....-P.T.R.Q.....V.T.K.....L.....
IV	.....RS.....G.....K.....

## Transframe Protein

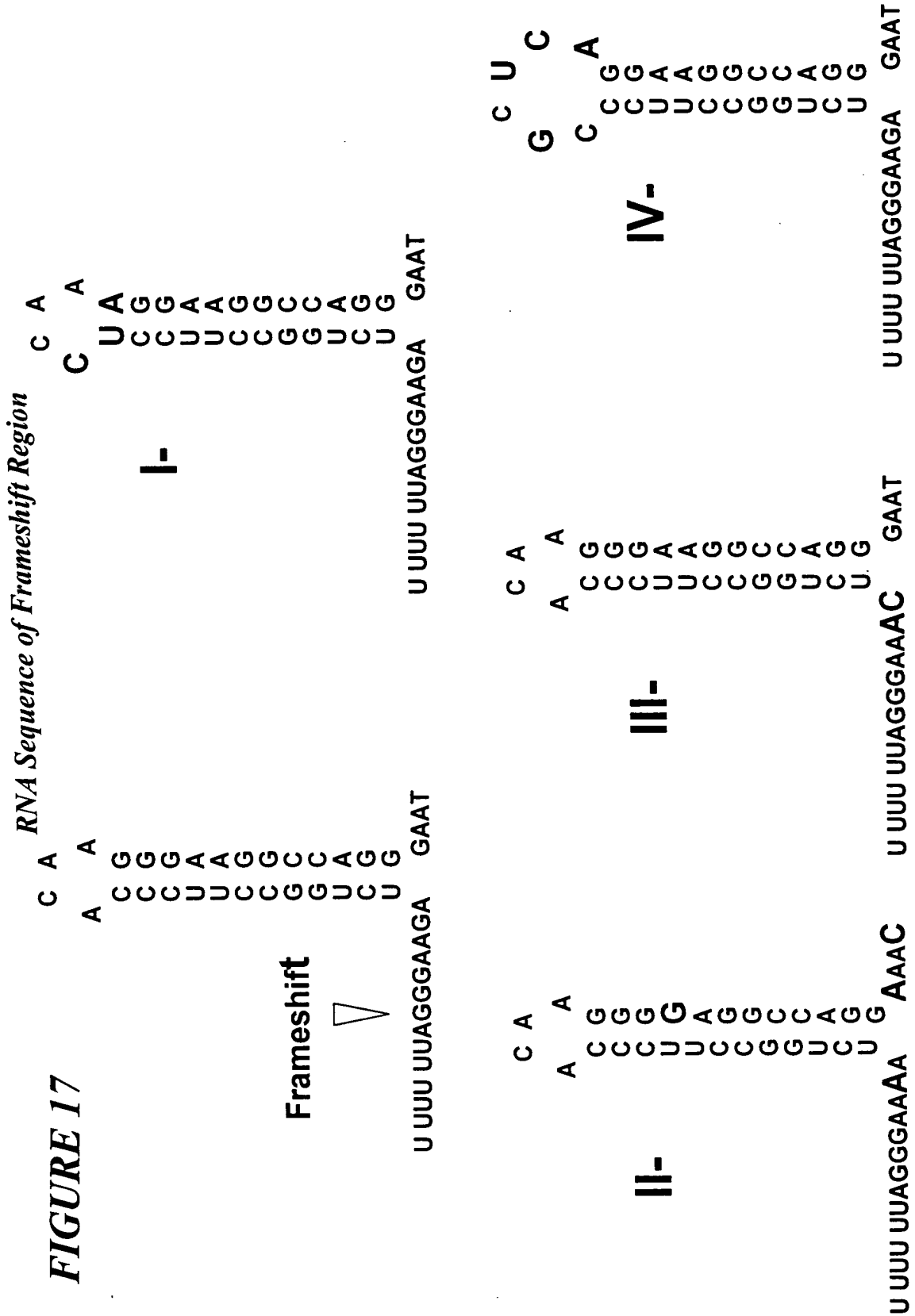
FFREDLAFPO GKAREFSSEQ TRANSPTRRE LQVWGRDNNS LSEAGADRQT VSFSE

I	.....L. R.....S.....N.....NL
II	.....N.....E..KLC...TI...S.....D.....
III	.....T.....P...N.....G.....-P.D.....I..CN.
IV	.....N.....L R.....T.....

\* I to IV represent clones derived from patient sample pools that retained the HS to PI



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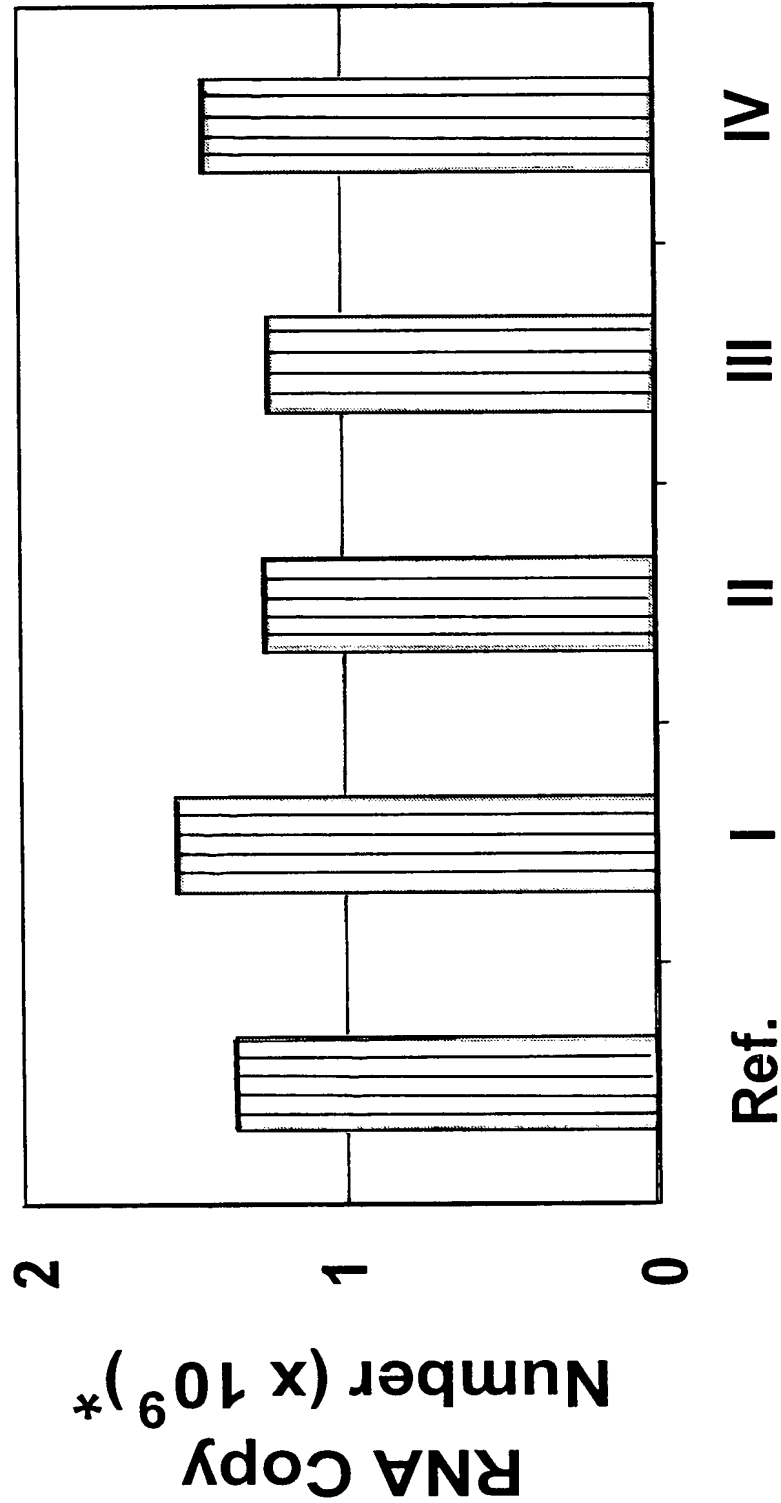






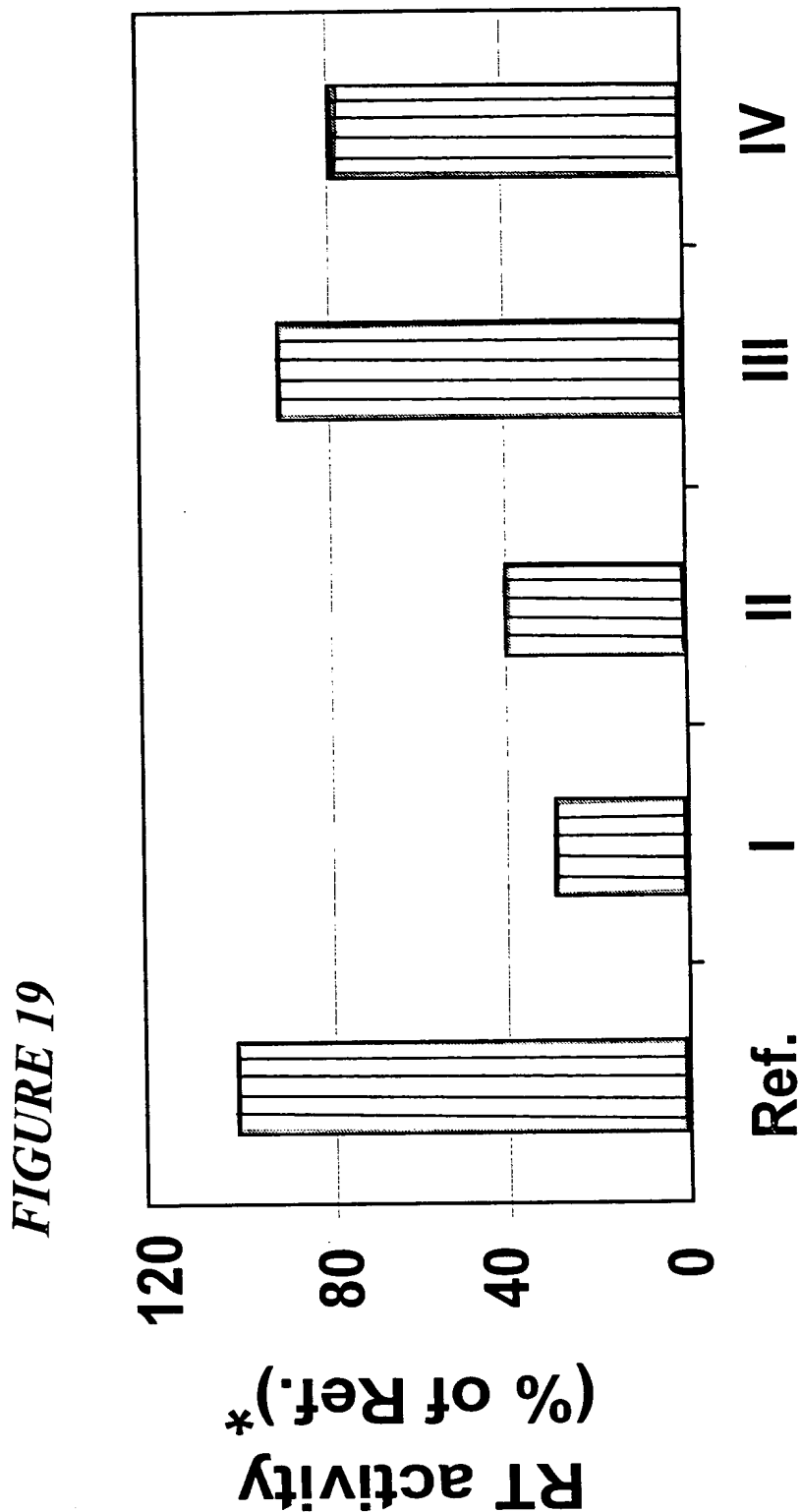
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FIGURE 18



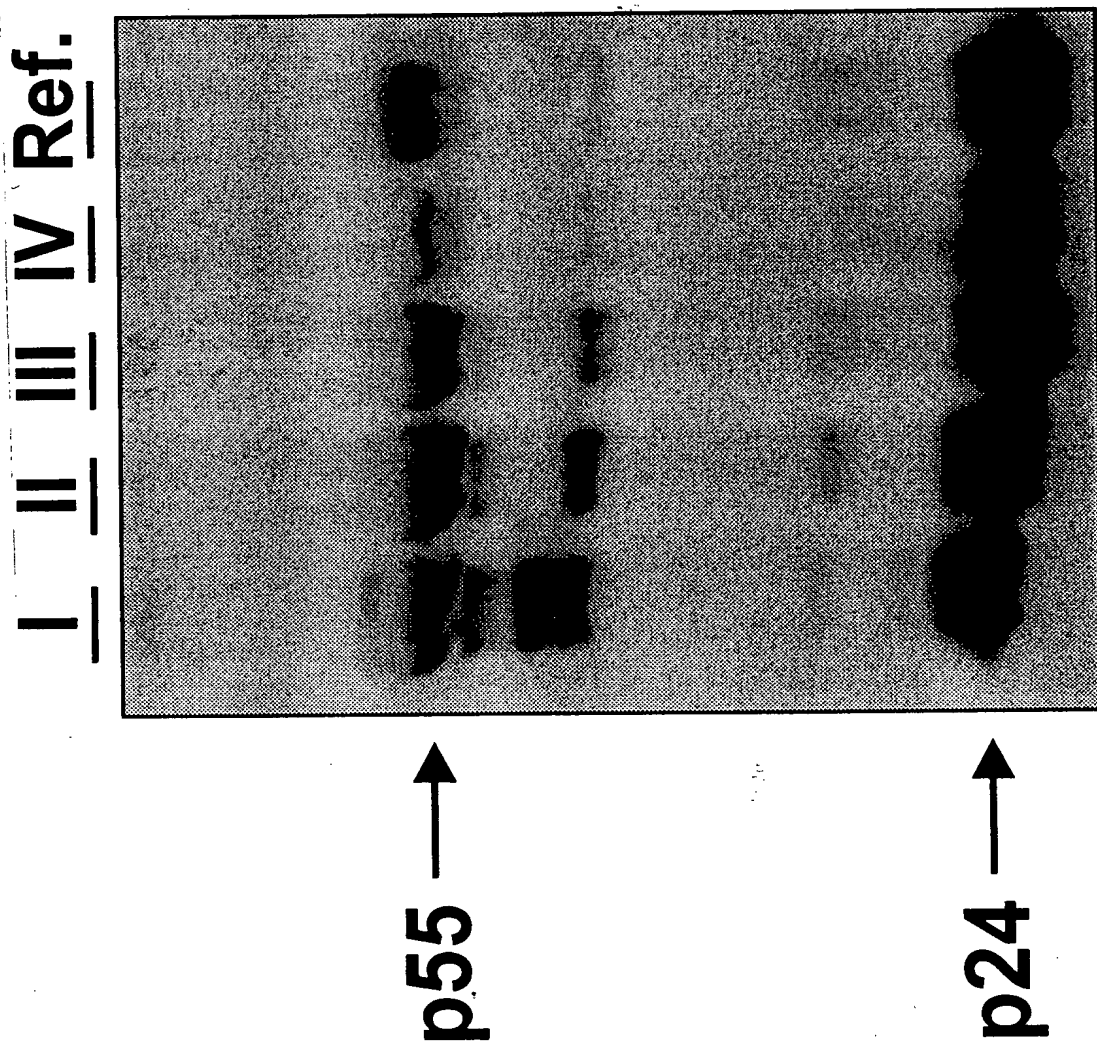


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**FIGURE 20**  
Processing of Pr55Gag in Virions  
Western Blot analysis using anti-p24 antibodies





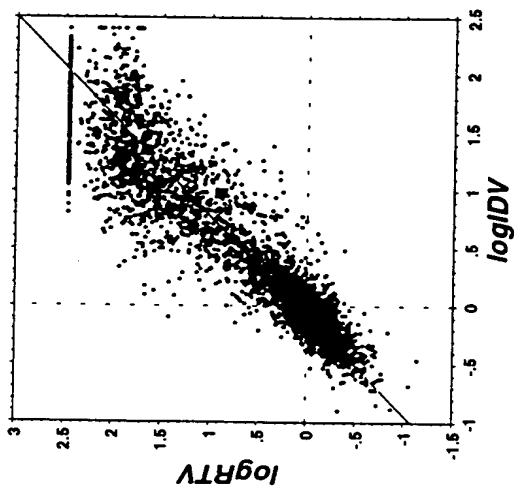
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**FIGURE 21**

- HS to PIs is associated with decreased viral fitness
- In 25% of the cases analyzed in this study, the HS to PIs and decreased replication capacity was attributed to mutations in gag sequences flanking the N-terminus of PR
- Genotypic analysis revealed several unusual polymorphisms in p1-p6/TFP-p6\* sequences
- Recombinant viruses carrying only the C-terminal gag sequences from patient isolates that retained the HS phenotype are released efficiently from the cell. However, analysis of the virus associated RT and PR activities suggest maturation defects

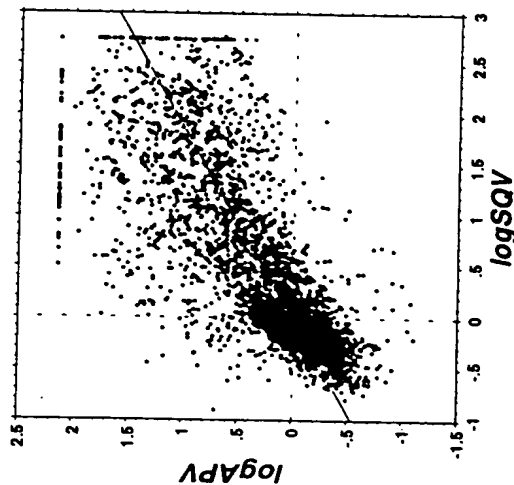


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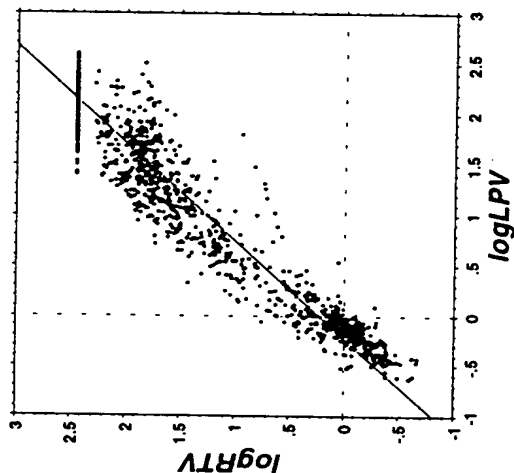
IDV vs. RTV

$R^2=0.867$



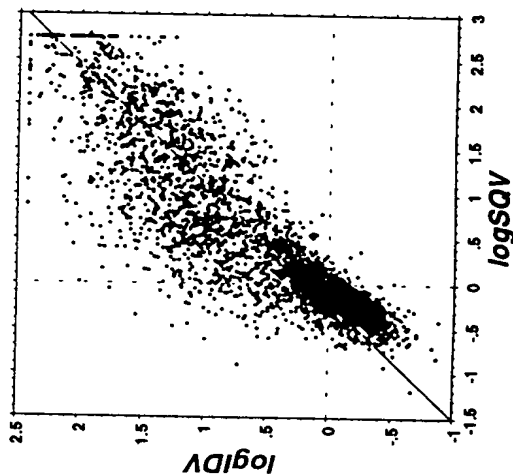
APV vs. SQV

$R^2=0.591$



LPV vs. RTV

$R^2=0.921$



IDV vs. SQV

$R^2=0.784$

FIGURE 22

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FIGURE 23

$R^2$  values  
(sorted by drug)

PI 1	PI 2	$R^2$
APV	IDV	0.675
APV	LPV	0.777
APV	NFV	0.544
APV	RTV	0.737
APV	SQV	0.591
IDV	LPV	0.849
IDV	NFV	0.774
IDV	NFV	0.925
IDV	RTV	0.867
IDV	SQV	0.784
NFV	LPV	0.757
NFV	RTV	0.696
NFV	RTV	0.873
NFV	SQV	0.691
NFV	SQV	0.801
RTV	LPV	0.921
RTV	SQV	0.740
SQV	LPV	0.678

$R^2$  values  
(sorted by drug)

PI 1	PI 2	$R^2$
IDV	NFV	0.925
RTV	LPV	0.921
RTV	SQV	0.880
NFV	RTV	0.873
IDV	RTV	0.867
IDV	LPV	0.849
NFV	SQV	0.801
IDV	SQV	0.784
APV	LPV	0.777
IDV	NFV	0.774
NFV	LPV	0.757
RTV	SQV	0.740
APV	RTV	0.737
NFV	RTV	0.696
NFV	SQV	0.691
SQV	LPV	0.678
APV	IDV	0.675
APV	SQV	0.591
APV	NFV	0.544

$R^2$  values for pairwise comparisons (all samples)

	APV	IDV	LPV	NFV	RTV	SQV
APV	1	0.675	0.777	0.544	0.737	0.591
IDV	0.675	1	0.849	0.774	0.867	0.784
LPV	0.777	0.849	1	0.757	0.921	0.678
NFV	0.544	0.774	0.757	1	0.696	0.691
RTV	0.737	0.867	0.921	0.696	1	0.740
SQV	0.591	0.784	0.678	0.691	0.740	1

<0.7

0.7-0.8

0.8-0.9

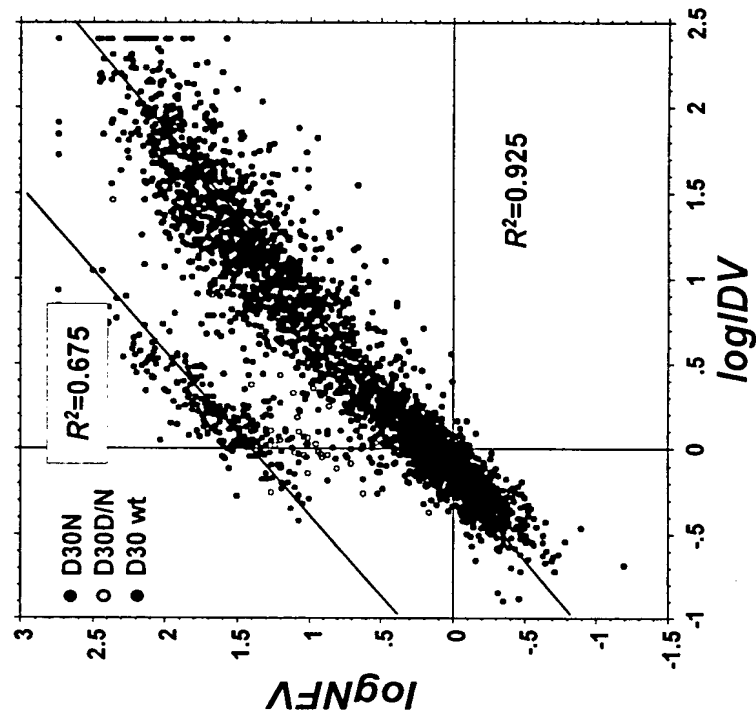
>0.9

\* Excluding viruses with D30N (see Fig. 4)

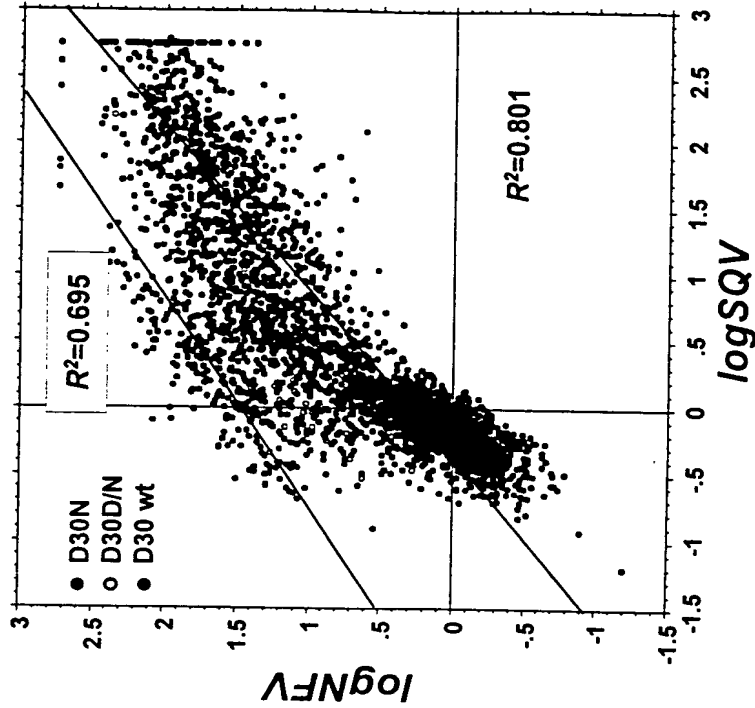
\*\* Excluding viruses with V82AFST (see Fig. 5)

**FIGURE 25**

**NFV vs. IDV, split by D30N**



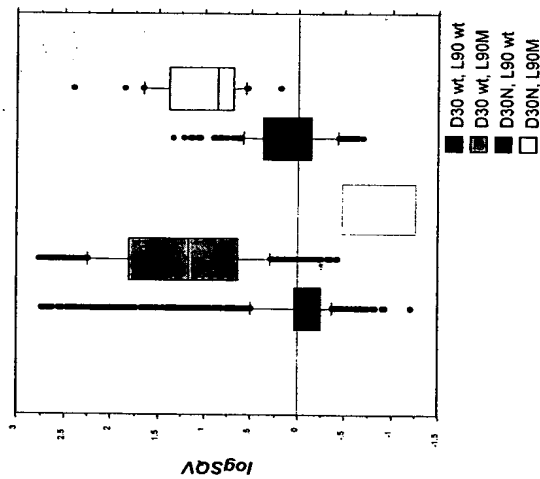
**NFV vs. SQV, split by D30N**



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FIGURE 26

SQV fold change +/- D30N, L90M



Phenotypes of samples containing D30N, and/or L90M; from the database (boxes contain a bar at the median and represent the 25<sup>th</sup> to 75<sup>th</sup> percentiles; the error bars represent the 10<sup>th</sup> and 90<sup>th</sup> percentiles; and the dots are the outliers.

D30N/N88D/L90M: Patient samples

PR genotype (resistance-associated mutations)	Fold change in IC <sub>50</sub> reference				
	AMP	IDV	NFV	ATV	SQV
L101V, D30N, L33UF, M36I, L63P, A71T, N88D, L90M	1.9	2.3	160.4	9.2	96
D30N, L63P, V77I, N88D, L90M	1.3	3.2	74.2	6.6	7.5
D30N, M36I, L63P, A71T, N88D, L90M	1.1	3.3	124.0	9.3	6.0
D30N, L63P, V77I, N88D, L90M	2.0	5.3	57.0	3.0	9.3
L10F, D30N, L33F, I54L, L63P, A71V, V77I, N88D, L90M	11.4	1.1	108.8	4.0	6.3
L10FY, D30N, I54L, L63P, A71T, V77I, N88D, L90M	3.7	3.9	171.4	6.3	38.1
D30N, L63P, V77I, N88D, L90M	0.4	1.3	32.8	2.1	3.7
L10F, D30N, L63P, A71T, V77I, N88D, L90M	2.3	3.7	217.5	3.9	11.9
L10LR, D30N, M36I, I54M, L63P, A71V, N88D, L90M	2.2	5.2	140.1	10.2	21.0
D30N, M36I, I54V, L63P, A71V, N88D, L90M	1.5	5.3	218.5	16.8	24.3
K20K/R, D30N, M36I, F53F/L, I54V, L63P, A71V, N88D, L90M	2.3	3.4	>550	35.0	72.0
L10LF, I130V, L19T, D30N, R41K, L63P, N88D, L90M	1.2	1.7	46.9	2.3	5.7
D30N, L63P, V77I, N88D, L90M	1.0	2.3	66.8	3.3	3.6
L10F, K20T, D30N, L33F, M36I, M46M/I, I54L, L63P, A71V, V77I, N88D, L90M	27.6	6.8	>550	31.2	45.3
D30N, L33F, L63P, A71A/T, N88D, L90M	1.3	1.3	35.7	2.7	6.5
D30N, L63P, V77I, N88D, L90M	1.5	3.5	73.7	3.3	5.2
D30N, M36I, I54V, L63P, A71V, N88D, L90M	2.2	12.0	140.4	27.0	45.8
L10F, K20R, D30N, V32V/I, L33U/F/I, M36I, M46I, I47I/V, I54I/A/M/T/V, L63P, A71V, V82V/A, N88D, L90M	>130	>250	>550	>275	257.5

Phenotypes of samples containing D30N, N88D, and L90M. There are no mixtures detected at these sites, indicating that the mutations are linked. All have reduced susceptibility (>2.5-fold change in IC<sub>50</sub>) to NFV and SQV.

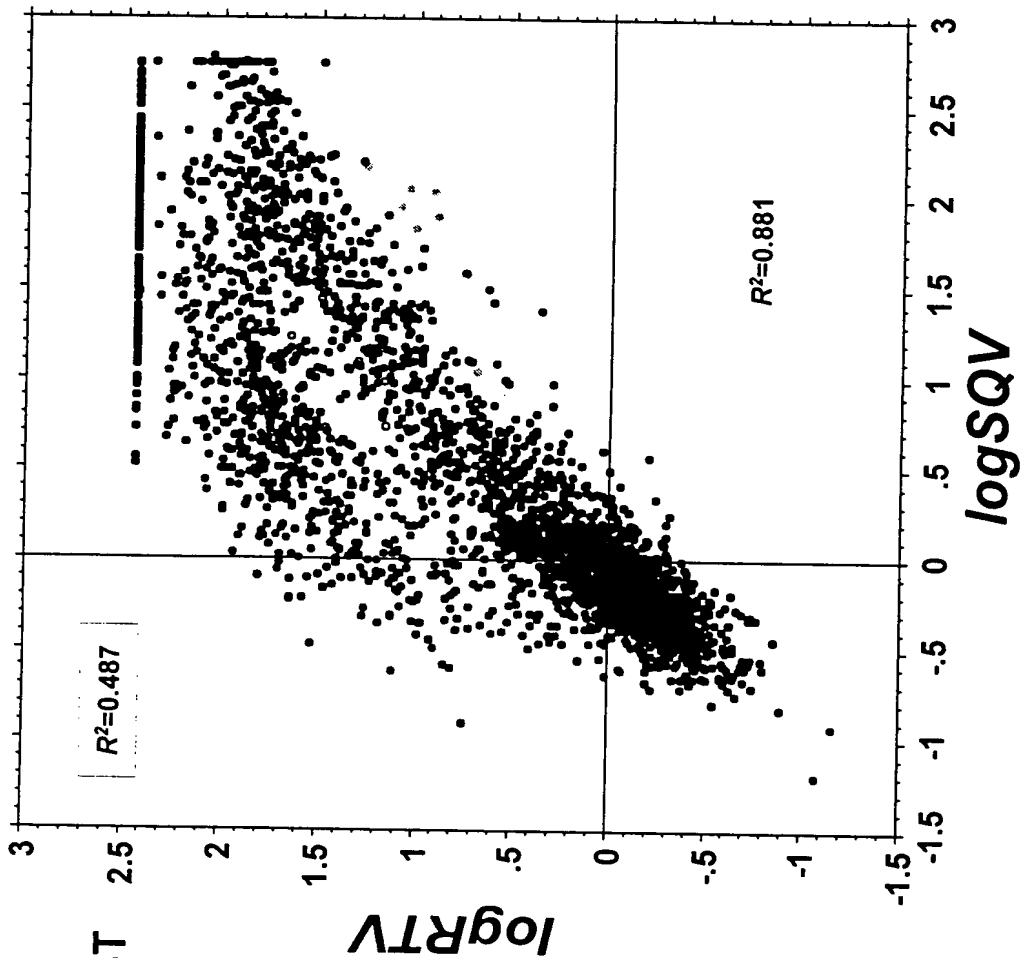




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FIGURE 27

SQV vs. RTV,  
split by V82AFST  
and G48V





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FIGURE 28

